

From AGING RESEARCH CENTER (ARC)
DEPARTMENT OF NEUROBIOLOGY, CARE SCIENCES AND SOCIETY
Karolinska Institutet, Stockholm, Sweden

CARDIOVASCULAR RISK FACTOR PROFILES IN THE DEVELOPMENT AND PROGRESSION OF PHYSICAL LIMITATION IN OLD AGE: A POPULATION-BASED STUDY

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**Karolinska
Institutet**

Stockholm 2018

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Published by Karolinska Institutet.

Cover illustration: © “Heart & Sole” by Vincent MacCracken Heiland

Printed by EPrint AB 2018

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ISBN 978-91-7831-054-8

CARDIOVASCULAR RISK FACTOR PROFILES IN THE DEVELOPMENT AND PROGRESSION OF PHYSICAL LIMITATION IN OLD AGE: A POPULATION-BASED STUDY

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Doth the ploughman plough all day to sow? Is he all day opening and breaking the clods of his land?
Doth he not, when he hath levelled the face thereof, cast abroad dill, and scatter cummin, and set the
wheat in rows, and the barley in an appointed place, and the rye in its border?
His God doth instruct him in his discretion, he doth teach him.

Isaiah chapter 28, verses 24 to 26, the Bible



Opportunity (place) + time (seed) + patience (rain and sun) = Great Harvest

Preservation of independence has been reported to be highly desired by older adults, even more than longevity. However, subclinical cardiovascular pathology can threaten a healthy older adult's maintenance of physical function. Therefore, the aim of this thesis was to investigate the role and potential neuropathological mechanisms of cardiovascular disease-related risk factors in the development of physical limitation and disability in older adults. Data were taken from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) for the initial three studies and from the embedded SNAC-K MRI sub-study for the final study.

Study I. Over six years of follow-up, of the 1971 persons free of disability in activities of daily living (ADL) at baseline, 119 (6.0%) persons developed ADL-disability. Limitation in both the one-leg balance stand (<5 sec.) and walking speed (<0.8 m/s) tests at baseline were associated with increased risk of future ADL-disability, but having both simultaneously showed a 10-fold higher likelihood of future ADL-disability.

Study II. In a sample free of cardiovascular diseases (CVDs) and physical limitation at baseline (n=1441), a greater cardiovascular risk burden, defined by the Framingham general cardiovascular risk score (FRS), was associated with increased risk of walking speed limitation over nine years of follow-up, but only in the younger-old adults (60-72 years old), not in the older-old (≥ 78 years old) (Hazard Ratio [HR] 1.09, 95% confidence interval [CI] 1.02–1.17; HR 0.98, 95% CI 0.92–1.03, respectively). Moreover, the FRS was not associated with future balance performance or muscle strength.

Study III. In the sample free of CVD and ADL-disability at baseline (n=1756), among the younger-old adults, physical inactivity (HR 4.10, 95% CI 1.22-13.76), diabetes (HR 5.61, 95% CI 1.17-26.82), and high C-reactive protein (HR 2.78, 95% CI 1.07-7.22) were associated with disability over nine years of follow-up. Among the older-old (≥ 78 years old), only physical inactivity was associated with greater risk of ADL-disability (HR 1.99, 95% CI 1.36-2.93), and walking speed modified this association, such that being physically inactive and having walking speed limitation, concomitantly, showed an even higher risk of ADL-disability.

Study IV. A faster average annual decline in walking speed over nine years of follow-up, in older adults free of walking speed limitation at baseline (n=331), was observed for those with greater volumes of white matter hyperintensities (WMH) at baseline, or having a higher burden of brain abnormalities (WMH+lacunes+ perivascular spaces).

Conclusion. Cardiovascular risk factors increase the risk of future physical limitation and disability, and brain abnormalities explain part of the underlying pathology driving the decline in physical function. However, risk profiles may differ between age groups of older adults, which suggests that interventions targeting decreasing cardiovascular risk may be more beneficial among younger-old adults, while older-old may benefit more from the maintenance of physical function.

Key words: physical performance, disability, activities of daily living, chronic disease, cognitive function, Framingham general cardiovascular risk score, physical function, cardiovascular disease, risk factors, ICF, cerebral small vessel disease, walking speed, magnetic resonance imaging (MRI).

Att behålla sin självständighet är viktigare för äldre personer än att leva ett långt liv. Men, subklinisk kardiovaskulär patologi kan försämra en frisk äldre persons möjlighet att bibehålla sina fysiska funktioner. Därför var målet med denna avhandling att studera rollen, och potentiella neuropatologiska mekanismer, av kardiovaskulära sjukdomsrelaterade riskfaktorer i utvecklingen av försämrad fysisk funktion och nedsättning i aktiviteter i dagliga livet (ADL) hos äldre personer. Data från Swedish National study on Aging and Care in Kungsholmen (SNAC-K) användes för de första tre studierna och SNAC-K MRI substudie användes för den sista studien i avhandlingen.

Studie I. Bland personer utan funktionsnedsättning i ADL vid den initiala bedömningen i början av SNAC-K studien (baslinje n=1971), utvecklade 119 (6,0%) personer funktionsnedsättning i ADL över en uppföljningsperiod på sex år. Funktionshinder i både balans (enbensstående <5 sek) och gånghastighet (<0.8 m/s) testat vid baslinje var associerat med ökad risk för framtida funktionsnedsättning i ADL, och att ha båda samtidigt visade en 10 gånger större risk för framtida funktionsnedsättning.

Studie II. Bland personer utan kardiovaskulära sjukdomar och funktionshinder vid baseline (n=1441) var en ökning av kardiovaskulär risk enligt Framingham general cardiovascular risk score (FRS) associerat med en större risk av försämrad gånghastighet över nio års uppföljning, men bara bland de yngre-äldre (60-72 år) (Hazard Ratio [HR] 1.09, 95% konfidens intervall [CI] 1.02–1.17), inte bland äldre-äldre (≥ 78 år) (HR 0.98, 95% CI 0.92–1.03). FRS var inte relaterat till en framtida balansförmåga eller muskelstyrka.

Studie III. Bland personer utan kardiovaskulära sjukdomar och funktionsnedsättningar i ADL vid baseline (n=1756), var fysisk inaktivitet (HR 4.10, 95% CI 1.22-13.76), diabetes (HR 5.61, 95% CI 1.17-26.82) och hög C-reactive protein (HR 2.78, 95% CI 1.07-7.22) associerat med funktionsnedsättning i ADL över en uppföljning på nio år bland de yngre-äldre. Emellertid, bland äldre-äldre var enbart fysisk inaktivitet associerat med en högre risk för att utveckla ADL-funktionsnedsättning (HR 1.99, 95% CI 1.36-2.93), samt att en kombination av inaktivitet och en långsam gånghastighet visade en ännu högre risk för att utveckla funktionsnedsättning i ADL.

Studie IV. Äldre personer utan funktionshinder i gånghastighet vid baslinje (n=331) som hade en större volym av hyperintensiteter i vit hjärnsubstans (WMH) utvecklade en snabbare genomsnittlig försämring i gånghastighet över nio år. En högre börda av hjärnabnormaliteter (WMH, lacunes, perivaskulära spatier) vid baslinje gav samma resultat.

Slutsatser. Kardiovaskulära riskfaktorer ökar risken av försämring i fysiska funktioner och funktionsnedsättning i ADL. Hjärnabnormaliteter förklarar delvis den underliggande patologi som driver försämringen i fysiska funktioner. Men riskprofiler skiljer sig mellan åldersgrupper bland äldre personer, således borde interventioner som syftar till att minska kardiovaskulär risk riktas mot den yngre-äldre befolkningen, medan interventioner med syfte att bevara god fysisk funktion skulle kunna göra mer nytta för de äldre-äldre.

Nyckelord. Fysisk prestationsförmåga, funktionsnedsättning, aktiviteter i dagliga livet, kroniska sjukdomar, kognitiv funktion, Framingham general cardiovascular risk score, fysisk funktion, kardiovaskulära sjukdomar, riskfaktorer, ICF, hjärn-kärlsjukdomar, cerebrala mikroangiopatier, gånghastighet, magnetisk resonanstomografi.

LIST OF SCIENTIFIC PAPERS

- I. Emerald G. Heiland, Anna-Karin Welmer, Rui Wang, Giola Santoni, Sara Angleman, Laura Fratiglioni, Chengxuan Qiu. Association of mobility limitations with incident disability among older adults: a population-based study. *Age & Ageing*, 2016, 45:812-819.
- II. Emerald G. Heiland, Chengxuan Qiu, Rui Wang, Giola Santoni, Yajun Liang, Laura Fratiglioni, Anna-Karin Welmer. Cardiovascular risk burden and future risk of walking speed limitation in older adults. *Journal of the American Geriatrics Society*, 2017, 65:2418-2424.
- III. Emerald G. Heiland, Anna-Karin Welmer, Rui Wang, Giola Santoni, Laura Fratiglioni, Chengxuan Qiu. Increased risk of disability in older adults with cardiovascular risk factors: variation by age and functional status. *Manuscript submitted*.
- IV. Emerald G. Heiland, Anna-Karin Welmer, Laura Fratiglioni, Grégoria Kalpouzos, Anna Laveskog, Rui Wang, Chengxuan Qiu. Walking speed decline in older adults in relation to cerebral small vessel disease: a population-based study. *Manuscript*.

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
BMI	Body mass index
CI	Confidence interval
CRF	Cardiovascular risk factor
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
FRS	Framingham general cardiovascular risk score
HDL	High-density lipoprotein
HR	Hazard ratio
ICF	International Classification of Functioning, Disability and Health
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
OR	Odds ratio
PAR	Population attributable risk
PVS	Perivascular spaces
SBP	Systolic blood pressure
SNAC-K	Swedish National study on Aging and Care in Kungsholmen
SPPB	Short Physical Performance Battery
SVD	Cerebral small vessel disease
WHO	World Health Organization
WMH	White matter hyperintensities

1 INTRODUCTION

1.1 POPULATION AGING AND DISABILITY

The World Health Organization (WHO) estimated that in 2010, 524 million people, making up 8% of the world's population, were aged 65 years and older. By 2050 this number is expected to triple to 1.5 billion, representing 16% of the global population, with the majority living in developed countries (1,2). Those 80 years and older are the fastest growing group, making up 1% of the global population, and are expected to reach 4.1% in 2050. However, in Sweden the population of those 80 years and older has already reached over 5% (3). Life expectancy and the aging population during the 20th century is continuing to rise into the 21st century. From 2002 to 2014, life expectancy has increased from 17.8 years to 20 years among those 65 years old in 27 European Union (EU) countries, and is expected to continue to grow rapidly in developed countries (4).

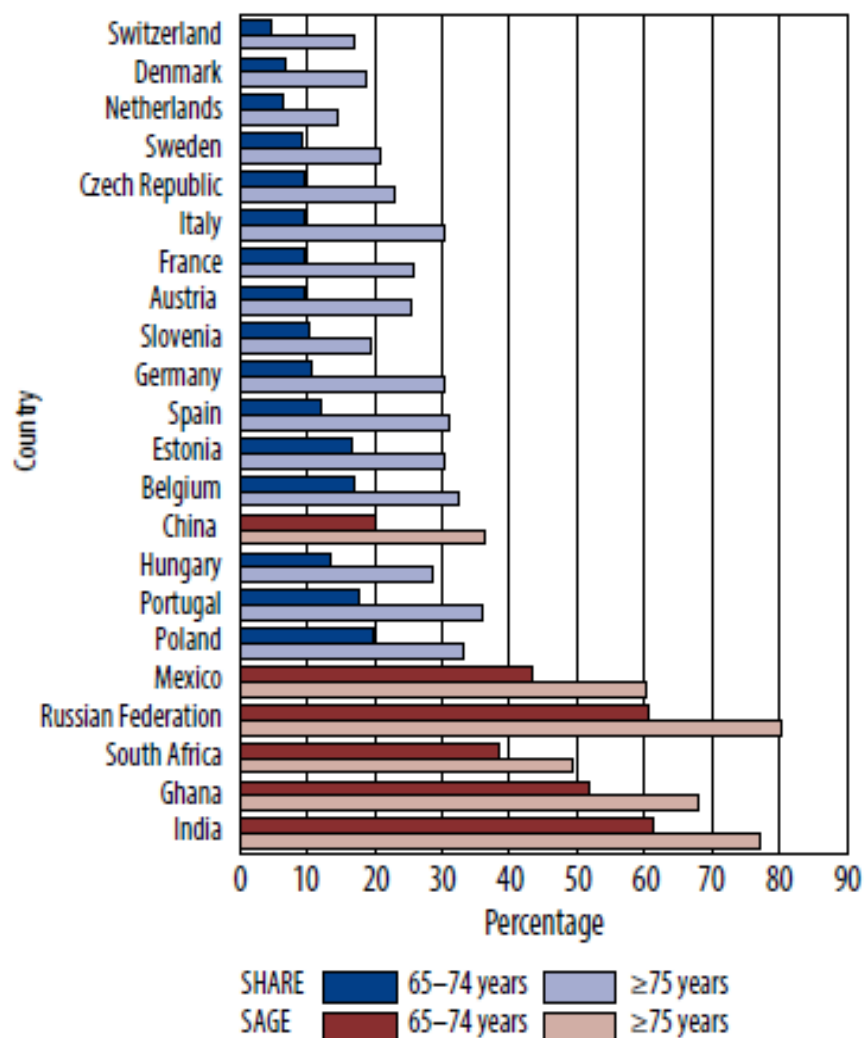


Figure 1. Proportion of adults with limitation in at least one of the five activities of daily living aged 65-74 and aged 75 years or older, by country. SHARE, Survey of Health, Ageing and Retirement in Europe; SAGE, Study on global AGEing and adult health. Source: World Health Organization (5).

These demographic transitions will result in a tremendous number of older adults being dependent on others for their personal care needs. Independent management of basic daily care activities, as long as possible, in older adults will help in the maintenance of a good quality of life, and deter burdens on families, thus decreasing societal health care costs (6). These fundamental basic or self-care activities of daily living (ADL) include: feeding, dressing, bathing or showering, toileting, transferring from bed and chair, and incontinence. However, incontinence is often suggested to be a reflection of organ dysfunction rather than a physical function impairment (7), thus it is usually excluded as an ADL limitation in many studies. The basic ADL scale was originally defined by the geriatrician Dr. Sidney Katz in 1963, to aid physicians in tracking the illness and function of patients, in order to provide appropriate care needs, and develop specific treatments. The use of the ADL scale continues today as a primary assessment of disability in older persons (8).

Figure 1 illustrates the age differences in the prevalence of ADL-disability across different countries (5). There is a clear variation across the countries in regards to the prevalence of ADL-disability. Also, there is a significantly greater percentage of people needing care in at least one activity in those 75 years old and above than those 65 to 74 years old. Different population-based studies have reported the incidence of disability, ranging from 4.9-47.0% (9-17). Specifically, it was reported in a Swedish population of adults 78 years and older that the incidence of ADL-disability was 10.6% after three years, and 28.1% after six years (18). Similarly, the Rotterdam study (age 55+) reported an incidence of 26.7% after six years of follow-up (15), whereas, an Italian cohort of adults 65 years and older, estimated disability incidence to be 7.3% after three years (19).

Temporal trends

Trends of increasing prevalence rates of disability among older adults have been reported in some studies (20-23). For example, the Spanish National Health Survey reported that the probability of disability has increased by 13% from 2000 to 2006 in 21 058 persons 64 years and older (24). On the contrary, reductions or stability in disability prevalence have been detected in other population-based studies (24-27). A Swedish study reported that over the past two decades the prevalence and incidence of ADL-disability has stayed stable, with a tendency towards a slow decrease (28). A downward trend in disability has also been observed in other countries, such as in Japan (25), China (29), and USA (25,26,30). In summary, the trend for disability is difficult to predict and little is known about its course at the end of life. For example, it is suggested that the trend is mostly mixed, with both improvement and worsening being reported (31,32). Nevertheless, considering the rapid rise in the proportion of persons aged 65 years and older, and especially those 85+ years, the total number of people with disability will definitively increase in the future. Thus, research should strive towards gaining a deeper comprehension into the underlying pathways describing loss of physical function, with the aim of pin-pointing meaningful moments of intervention, and identifying specific and modifiable factors in order to prevent or delay the onset of disability.

1.2 PHYSICAL LIMITATION AND DISABILITY

A key method in reducing the healthcare costs and helping older persons maintain independence into more advanced old age is through preservation of physical function. It has been estimated that at least half of end-stage disability is due to a progressive functional decline, while the other part results from acute clinical events (33). Decline in physical function, characterized by poor physical performance, is a prodromal period of disability (34), therefore, an ideal window of opportunity for the implementation of interventions to help older adults remain functionally independent longer.

Conceptually, this project has been framed around the WHO's International Classification of Functioning, Disability and Health (ICF) model, which was developed in 2001 to illustrate human function and the dynamic play between constructs (**Figure 2**) (35,36). The ICF model will be used as a framework, providing a compound view of health without any assumptions on causality. Models of disability have been developed in order to help clarify the underlying processes that may lead to disability and to identify points of prevention and rehabilitation. Disability is not explicitly defined in the ICF model, but for this project it has been defined in accordance to the gerontological literature as dependence in activities of daily living (7,37) and has been categorized in the ICF model's domain of "activity". Particularly, for this project I have focused more on the medical and biological perspective of aging, proposing an age-related progressive deterioration of physical function (38). Using this perspective of the universal ICF model, we can understand the risk factors and underlying pathological processes (ICF domains of "health condition" and "body functions") leading to disability. Physical limitations are classified as "body functions" in the ICF model and are considered as detached from a situation context (e.g. walking speed, balance) and disability as a situational variable (e.g. dependence in dressing, bathing, and feeding). Using this definition, disability is the result of a progressive decline in an individual's capacity due to a synergistic effect between health conditions and contextual factors (35). This supports the idea that poor physical performance may indicate intermediary stages from exposures to risk factors, through pathology/impairments to the onset and progression of disability.

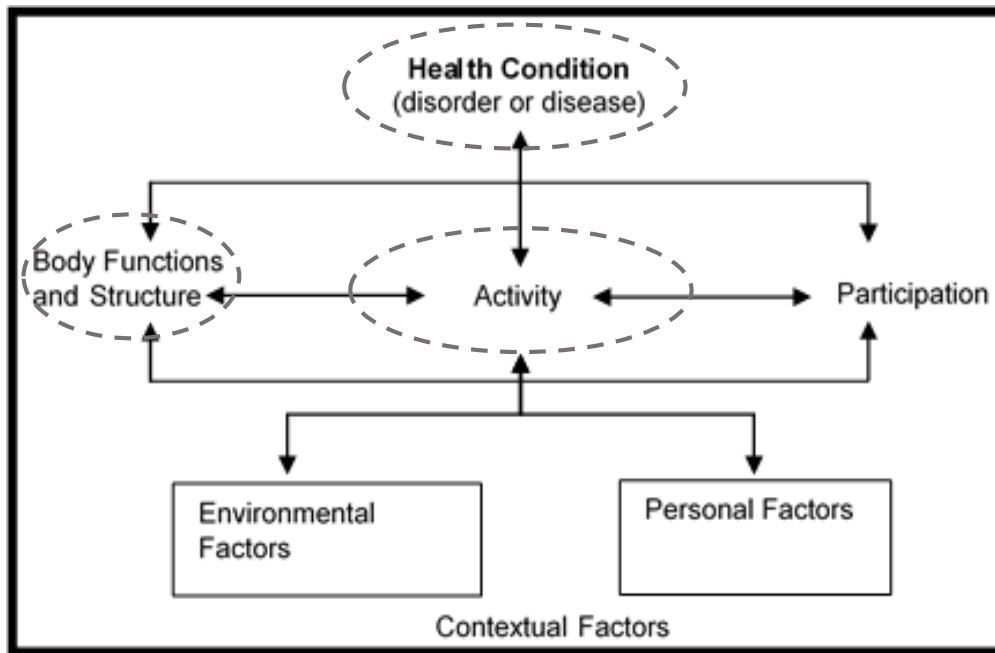


Figure 2. International Classification of Functioning, Disability, and Health (ICF) model proposed by the World Health Organization) (36). Perforated circles represent areas focused on in this thesis.

Physical performance tests (e.g. walking speed, balance, chair stand) provide pragmatic, appealing, valid, sensitive, and objective perspectives of physical function, owing to their minor influence from culture, language, and education (39). Also, these tests have low administration burden, therefore ideal for clinical and epidemiological settings as part of the geriatric assessment. These standardized measures can characterize different gradients of physical function and demonstrate strong predictability of future health status and adverse outcomes, such as nursing home admission and mortality, in clinical and epidemiological studies (40-44). In nondisabled persons, and even in high functioning individuals, physical performance assessments are able to discriminate between quite high functioning individuals (45,46). Furthermore, these tests may also predict disability, with the most recent studies summarized in **Table 1**. Walking speed has been most often investigated in relation to disability, with the other physical functions being neglected. Investigation into the other physical functions can offer more information regarding the different levels of physical function. Consequently, greater understanding can be gained into the temporal order of physical function loss and their predictability of future disability. Yet, further investigation is required, particularly in regards to mobility.

Lower extremity function limitation

Limitations in lower extremity function, such as mobility, is suggested to indicate a reduced reserve capacity early in the pathways to disability, increasing vulnerability (34). Aging is overall associated with a slowing of movement and diminished lower extremity function (47), yet in humans, locomotion is involved in most activities one must undertake every day to maintain independence and a good quality of life. Therefore, measures of mobility can provide

insight into health and function in aging and the disease progression. For instance, mobility limitation has also been shown to be associated with cognitive impairment (48,49). Within the mobility measures, a progression of decline has been suggested, where balance deteriorates prior to walking speed (50). The walking speed test has been demonstrated to be the most predictive of disability even in high-functioning older adults (51) and in the older-old (52). Yet, the hierarchical order in which each physical function declines and the extent of their predictive value has been rarely examined. This understanding might give a more accurate picture of the intermediate stages of disability loss and understanding of the different tests' properties. Investigation into mobility levels, including walking speed and balance, plus their risk differences, are reasonable starting points as they are also central components of physical performance batteries (e.g. Short Physical Performance Battery, SPPB) and comprise more broad lower extremity tests (e.g. Timed Up and Go).

Walking speed

Walking is a fundamental ability of daily human function and to maintain independence. The walking speed test is a known robust measure of physical function, and limitation in this test can predict several adverse outcomes, such as cognitive impairment, institutionalization, falls, and mortality (40,43,53), and is ubiquitous among the older population. Furthermore, walking speed limitation has also been demonstrated in several studies as an indicator of future disability (11,14,51,54-59). Guralnik et al. showed that measuring walking speed alone was nearly as predictive as performing a full battery of performance tests (i.e. chair stand, walking speed, grip strength, and balance) in assessing subsequent disability (51). Contrarily, one study found the walking speed test to be inferior to a full battery in predicting disability over three years in adults 65 years and older (19). Yet, most studies have exhibited walking speed's superiority. For example, a pooled analysis of seven different cohorts demonstrated walking speed's ability to predict incident disability in bathing or dressing over three years in 27 220 older adults 65 years of age and older (60). Walking speed has been named the 6th vital sign, due to its capacity to indicate health status, function, and future adverse outcomes, even in the absence of overt conditions (40,43,47,61). Of note, one study found that walking speed was a more sensitive predictor of disability in adults ≥ 75 years of age than those between 65 and 75 years of age (14), suggesting that there may be variations by age.

Walking speed is not only a robust marker, but also an attractive tool for utilization in both research and clinical settings, as it is easy to administer and requires little equipment. The distances usually performed (6 m or 4 m) are feasible in both settings (19,62), and avoids lower limb exhaustion and reduces in-test balance variations if done at a usual pace (62). Hence, the test is one of the most plausible to be performed in a geriatric assessment. Furthermore, clinically, the inherent biological phenomenon of walking speed in attesting disease, function, and the "vitality of life", reflects its robustness in exposing concealed conditions of organ systems (62). This should be a call to clinicians to examine beyond the walking speed test as only a measure of physical function, but also as an indicator of other potential health conditions, such as cardiovascular disease (CVD).

Balance

Balance also plays an important role in human gait. While moving, balance involves maintaining postural stability while keeping the center of mass over the center of pressure. In normal human gait there is a point of single stability, requiring input from physiological systems related to balance capabilities. With an increase in age there are also coinciding declines in visual, vestibular, and proprioceptive systems, which are all highly related to postural stability. However, balance in association with the risk of developing disability has not been studied independently (14,16,57,63), but instead combined in a score with other physical performance tests (14,16,19,51,64), neglecting a full understanding of the role of balance in relation to other measures. However, studies have been generally consistent in showing an association between poor lower balance performance and greater risk of disability. Particularly, the simple one-leg balance stand test (65) has been shown to be a good detector of older people at increased risk for future physical dysfunction (66,67), and can discriminate between high-functioning individuals (46).

Impairments in balance performance have been suggested to precede a decline in walking speed. This may be due to the sensory systems, such as vestibular and proprioceptive, declining early in the aging process, thus balance tends to demonstrate lower predictive power of disability than walking speed (14,52). Yet, two studies have shown the contrary, reporting balance to be of higher predictive power than walking speed (14,16). The reasons for these conflicting results are mainly due to the assessment tools used (16) and age differences (14). Nevertheless, balance is a plausible early indicator in the functional decline and progression to disability, but its position in the decline of physical function and predictive power are unclear.

Muscle strength

With advancing age comes also the reduction in muscle mass and strength (68). Lower extremity muscle strength in clinical and epidemiological settings is often measured with the five times sit-to-stand chair stand test. The chair stand test employs the participant to move from a sitting to standing position without the use of their arms as fast as possible. Although, this test incorporates various muscle groups (e.g. gluteus maximus and tibialis anterior) and physical abilities (e.g. balance, speed, and power) (69,70), it is mainly a test of quadriceps muscular strength for knee extension. Thus, impairment in the chair stand test has been correlated with sarcopenia – the age-related loss of muscle mass and strength, which can in turn increase the risk of disability (71). The task of going from bed to chair as part of the ADL, exemplifies the requirement of lower extremity muscular strength. Specifically, muscle groups of the lower limbs mainly perform concentric motions where a sufficient range of motion of the joints and power are required to fulfill the task. With increased velocity there is increased torque at the joints, particularly the hip, knee, and ankle. Thus, any limitation in the lower limb may affect performance on the chair stand test (72).

Poor performance on the chair stand test has also been shown to predict mortality in older adults (42), and injurious falls (73), but has been little studied with regards to other health outcomes. More frequently it has been included in a composite score along with walking speed and balance, such as the SPPB (51,74). These few studies, nevertheless did show the chair stand

test to predict disability (51,57,74,75). As well, one review reported chair stand test to be a significant predictor of disability (76). One study of Japanese older women found no difference in chair stand time for women who developed ADL-disability than those who did not (77). Additionally, Guralnik et al. showed that among adults 70 years and older limitation on the chair stand test predicted ADL-disability after four years (RR 4.1, 95% CI 2.3-7.2) (52).

It has been shown that the SPPB (including walking speed, balance, and chair stand) is associated with incident disability independent of muscle mass (64). Indeed, reduced muscle strength is more associated with worse functional capacity than muscle mass (78). However, slow walking speed and poor balance have been demonstrated to be more powerful predictors of disability than muscle strength (79). Therefore, it is essential to deconstruct the roles of different physical function measures and their related risk factors on future disability.

Table 1. A summary of major population-based longitudinal studies of various physical performance measures in predicting incident disability in activities of daily living.

Study, Year, Country	Study population	N	Age (years)	Follow-up Time (years)	Measures/tests	Main findings
Minnecci et al. 2015 (19), Italy	The Insufficienza Cardiaca negli Anziani Residenti a Dicomano Study	561	65+	3	SPPB, walking speed, and hand-grip strength	Incidence of disability was 7.3%. All predicted disability
Legrand et al. 2014 (64), Belgium	BELFRAIL study (BF _{C80+})	421	80+	2.8	SPPB	Multi-adjusted OR of 0.49 (95% CI 0.31–0.78)
Idland et al. 2013 (12), Norway	A community cohort of women	113	75-92	9	Functional reach, step climbing, and walking speed	25.7% disabled at follow-up. Walking speed was the strongest predictor (OR 0.40, 95% CI 0.02-0.69)
Cawthon et al. 2011 (80), USA	Health, Aging and Body Composition Study	2484	70-80	6	Strength (knee extension, grip strength), walking speed, and chair stands	Adiposity and physical performance, but not strength were associated with disability
Wennie Huang et al. 2010 (16), USA	Community cohort study	110	65+	2.5	SPPB, walking speed, Berg balance scale, grip strength, and timed up and go	Balance was the strongest predictor
Rosano et al. 2008 (58), USA	Cardiovascular Health Study	3156	65+	Median 8.4	Walking speed, and DSST	Lower DSST score and slower gait individually or combined were significantly associated with greater risk of incident disability
Onder et al. 2005 (57), USA	Women's Health and Aging Study	884	65+	3	Walking speed, balance, chair stands, putting on a blouse, Purdue pegboard test, and grip strength, and summary performance scores	All except grip strength predicted ADL-disability. Walking speed and summary performance scores showed the greatest predictability
Guralnik et al. 2000 (51), USA	EPESE and Hispanic EPESE	4588, 1946	65+	6	Balance, walking speed, chair stand, and summary performance score	Summary performance score or walking speed alone predicted disability
Shinkai et al. 2000 (14), Japan	Tokyo Metropolitan Institute of Gerontology Longitudinal Interdisciplinary Study of Ageing	949	65+	6	Walking speed, balance, and hand-grip	All predicted disability, but walking speed was most sensitive

*Only bathing and dressing in activities of daily living (ADLs) as outcome; SPPB: short physical performance battery; DSST: digit symbol substitution test; EPESE: Established Populations for the Epidemiologic Study of the Elderly; DXA: dual X-ray absorptiometry; CT: computed tomography; OR: odds ratio; RR: relative risk; CI: confidence interval.

1.3 CARDIOVASCULAR RISK FACTORS

Cardiovascular disease (CVD) is one of leading causes of death worldwide, contributing to 46.2% of all deaths in 2012 (81). Subclinical cardiovascular conditions, which may exist in younger and middle aged populations long before its clinical manifestation, can increase the risk of a future CVD event (82). The underlying process that results in CVD is atherosclerosis. This complex process can occur over several years or even decades, where fatty material and cholesterol are deposited inside the lumen of arteries. These deposits, known as plaques, disrupt the inner surface of the vessels, making it harder for blood to flow through. Blood clots rupturing in the coronary artery can lead to a cardiovascular event, like a heart attack, whereas in the brain can lead to a stroke (83). The factors that promote the process of atherosclerosis, defined by the WHO, and included in this project, are known as cardiovascular risk factors (CRFs), and include: 1) behavioural risk factors, including smoking, physical inactivity, harmful use of alcohol; and 2) metabolic risk factors, including raised blood pressure (hypertension), high body mass index (BMI), diabetes, and raised blood lipids (e.g. cholesterol) (83).

These CRFs are estimated to contribute to 90.4% of the population attributable risk (PAR) for myocardial infarction (84), with high total cholesterol, smoking, hypertension, obesity, and diabetes contributing 80% of the PAR. Particularly, it has been found previously in the SNACK population (which was utilized for this doctoral project) that the prevalence of some CRFs increased with age (e.g. hypertension and diabetes), while others decreased with age (e.g. obesity, high total cholesterol) (85). Therefore, these factors are feasible targets for prevention of CVD (84), but their risks may differ by age. A large percentage of CVDs can be avoided through improvements of cardiovascular risk profiles through interventions reducing behavioural and metabolic risk factors as defined by the WHO (83). These CRFs not only increase the risk of CVD, but also the risk of cognitive impairment in older adults (86). Thus, identification of at-risk persons can allow for subsequent implementation of appropriate procedures, according to their CRF profiles, to reduce the risk of future adverse health events.

1.4 CRFS, PHYSICAL LIMITATION, AND DISABILITY

CVD has been shown to contribute to a loss in physical function (34), and it has been estimated that over 25% of disability is attributable to CVD in older adults (87). The effect of CRFs on increasing the risk of CVD is well-established, while the association with future physical limitation and disability still requires some investigation, especially concerning individual and aggregated CRFs, and age variations. The subclinical atherosclerotic process may be indicated through diminishment in physical abilities in the absence of CVD, manifesting as deficiencies on various physical performance tests. **Tables 2 and 3** summarize the longitudinal population-based studies investigating the association between individual and combined CRFs and physical limitation or disability in older adults. Most of these investigations have explored the association between CRFs and walking speed or test batteries, ignoring other physical functions and disability. A systematic review has summarized the studies examining the association between CRFs and specifically walking speed in noninstitutionalized adults 60 years and older (62). They identified eight prospective studies, showing significant associations between CRFs and impaired walking speed, but there is much variation in the risk due to heterogeneity

between study protocols for the testing of walking speed. Furthermore, some CRFs are given more attention than others in association with physical limitation, such as physical activity, hypertension, and obesity.

Behavioural risk factors

Physical activity

Physical inactivity is a well-known risk factor for CVD and even more so in older adults. It is recommended by the WHO that older adults perform 150 minutes of moderate-intensity physical activity per week or 75 minutes of vigorous-intensity physical activity over a week or an equivalent combination. They are also recommended to perform physical activity to enhance balance and prevent falls, and perform muscle-strengthening activities two or more days a week (88). It is recognized that an active lifestyle is profitable in reducing the risk of morbidity and all-cause mortality. There is also a substantial economic benefit from leading an active life on a societal level. Globally in 2010, it has been estimated that 55% and 18% of older adults and younger adults, respectively, were insufficiently active (89). In Sweden it was reported that 28.7% of adults 18 years and older perform insufficient physical activity, according to the WHO recommendations (90). In the US, it has been estimated that 5.6 billion US dollars could have been saved from coronary heart disease if just 10% of US adults began a regular walking program. Yet, despite the awareness of the high costs and reduction in CVD risk from physical activity, the prevalence of physical inactivity remains high (91), and is on the rise, even more so among older adults.

The benefits of physical activity on improving physical function in population-based studies are well-known (92-96), although fewer studies demonstrated the positive effects on basic self-care ADL (92,97-99). However, these studies have consistently shown a beneficial effect of physical activity on future functional ability. Likewise, most studies have not been conducted in relatively healthy older populations (i.e. excluding those with chronic conditions, especially CVD). Randomized controlled trials have also revealed promising results of exercise interventions on improving physical function, but mainly in frail older adults (100,101). Research has shown that exercise, even if initiated late in life can have protective effects against disability and can possibly postpone it (102). In both a Mexican and American population-based study of adults a beneficial effect of physical activity on ADL-disability was demonstrated after two years of follow-up (102). In a cohort study of adults from 39 to 63 years of age, over 8.8 years of follow-up, showed that a physically active mid-life is important to maintain physical function in later life (103). Also, another study including American and British populations found that higher levels of physical activity in adults between 50 and 69 years of age were associated with lower risk of mobility impairment over six years of follow-up (95). However, not many studies have investigated this association in older-old adults (e.g., 80+ years). One meta-analysis of longitudinal studies of adults 50 years and older, examining the association between physical activity and incident disability (96), found that out of the nine studies, all but one showed a lower risk of disability in those who were physically active compared to those who were inactive. This was evident in both those <74 years old and those ≥75 years and older.

Alcohol consumption

Alcohol consumption in association with physical function and disability is less established. In the Whitehall II cohort study, they found that nonmoderate alcohol consumption (none/occasional or heavy) was associated with slower walking speed over 17 years of follow-up (104). Also, in the EPESE cohort, adults 65 years and older that did not consume alcohol compared to those who had a small to moderate intake had worse mobility after four years of follow-up (105). However, the contrary has also been shown in other studies finding no association with mobility limitation (106). Studies looking at other tests of physical performance than only walking speed, or distinguishing between them are generally lacking. An American study found that moderate alcohol consumption (five or more drinks per year without alcohol problems) was associated with improved physical performance, however it was a combined battery of physical performance tests of which walking speed, chair stand, balance, and grip strength were incorporated (107). Never consuming alcohol has also been shown to be associated with incident disability compared to those who were moderate consumers (98). Whereas another study found that there was no association between any levels of alcohol consumption and disability over 12 years of follow-up (92).

Smoking

Smoking cessation can have tremendous beneficial effects on health and is one of the most effective preventive measures against CVD. However, very few previous studies have looked at functional consequences of smoking among older adult populations (108), and longitudinally. The few studies that have investigated this association, have found current smoking to be associated with walking speed limitation (104,105), or poor overall physical performance (107). Also, smoking has been found to be associated with disability (92,97,98,107), but one study has also demonstrated a non-significant association with disability (109). The prospective Whitehall II cohort study showed that smoking was associated with poor physical function performance, although a weak association over 17 years of follow-up (104). The young- and middle-aged British 1946 Birth Cohort Study likewise found that greater smoking pack-years was related to reduced overall physical performance and poorer performance in balance and chair stand, even after controlling for other conditions (110). This too was observed in another study that exhibited a greater risk of losing mobility function after four years in adults 65 years and older who were current smokers (105).

Cardio-metabolic risk factors

Hypertension

It is estimated that about 1 billion individuals experience hypertension globally, and about 7.1 million deaths per year may be attributable to hypertension. Also, its prevalence increases with age, and the number of persons receiving hypertension treatment has increased considerably. Over half of adults between 60 and 69 years of age, and about three-fourths of adults 70 years and older experience hypertension (111).

High blood pressure has also been suggested to demonstrate a J- or U-shaped relationship with mortality in older age, such that both high and low blood pressure are associated with greater

risk of mortality (112). It is suggested that low blood pressure may be an indicator or consequence of frailty, as blood pressure tends to decrease prior to a critical event, such as death (112,113).

Hypertension has been found previously to be associated with a faster decline in physical function. In the Cardiovascular and Health Study including a cohort of adults 65 years and older, hypertension was associated with an accelerated decline in walking speed over 18 years of follow-up (114), independent of other risk factors in a well-functioning population. Similarly, in the Dijon Three-City study (115), and the Adult Changes of Thought Study (107), both found hypertension to be associated with incident slow walking speed over 3 to 18 years of follow-up. Yet, in the Health and Retirement Study of adults 65+, there was no association between hypertension and decreased walking speed over four years (106). Several studies have reported a rather consistent association between hypertension and a greater risk of disability (99,107,109,116).

Obesity

High BMI, particularly obesity, has been studied in relation to physical function and disability. Research has shown that two-thirds of adults, 60 years and older, are overweight and one-third are obese in the US (117). With aging there is a reduction in muscle mass, accompanied by an increase in fat mass. Higher fat mass has been previously shown to be associated with disability (118). Older adults who are obese have been found to experience disability in ADL about five years earlier and are twice as likely to develop physical limitation or disability (119). A review of longitudinal studies reported that together an accrual of adipose tissue with reduced skeletal muscle, impacts future development of functional impairments (120). Evidence suggests that obese older adults are characterized by having a lower strength to body mass ratio compared to their non-obese counterparts, predominantly for tasks that entail lower extremity strength, such as walking and rising from a chair (117).

A review of 15 longitudinal studies reported a relationship between adiposity and declining mobility. The studies consistently found that obesity compromised walking, stair climbing, and getting up from a chair (120). Other studies have also shown a significant association between obesity and mobility or walking speed limitation (106,121-124). A study of Finnish middle-age adults found that high BMI at baseline was associated with age- and sex-adjusted risk of walking speed limitation after 22 years (124). Correspondingly, several longitudinal studies examining the association between obesity and disability consistently showed an association between obesity and increased risk of disability (97,109,121,125,126). However, a U-shape or J-shape relationship has also been suggested between levels of BMI and the risk of disability (125), meaning that underweight may also be a risk factor for disability. Indeed, one study found that being underweight ($<18.5 \text{ kg/m}^2$) or obese ($>30 \text{ kg/m}^2$) were both associated with increased risk of disability (127).

Total cholesterol

Cholesterol is a biological molecule that is essential for maintaining cell membrane stability, and is also important for hormone and vitamin synthesis (128). Cholesterol is also a main player in atherosclerosis. There is a paucity, but also an incongruity, of research on high total cholesterol in association with physical function and disability. The Longitudinal Aging Study

of Amsterdam found no association between total cholesterol and functional status over three years in men, but discovered a significant association in women (129). Whereas the Framingham Disability Study showed no association between total cholesterol in midlife and disability over 27 years (109). However, high total cholesterol has been examined as a component of clustered CRFs, where associations were found between reduced burden of CRFs and improved physical performance (130-132) or reduced risk of disability (133,134).

Diabetes

Type II diabetes, hereafter termed diabetes, affects more than one in five older adults age 65 years and older (117), and its prevalence is on the rise globally. Diabetes is one of the most often investigated CRFs in relation to functional outcomes. A meta-analysis of nine longitudinal studies found that diabetes is strongly associated with disability, defined as basic or instrumental activities of daily living, or mobility limitation, with follow-ups ranging from 18 months to nine years (135). Four longitudinal studies in this meta-analysis that examined the risk of mobility limitation found that persons with diabetes were more likely to report physical limitation than those without diabetes. Only two studies were reported in the meta-analysis to have looked at ADL-disability, showing an increased risk of disability in those with diabetes (135). Overall, this meta-analysis found a 50-80% increased risk of disability among persons with diabetes compared to those without. Furthermore, in the Study of Osteoporotic Fractures, over 12 years of follow-up, women with diabetes were twice as likely to become disabled as persons without diabetes. Interestingly, age differences were also observed. The association between diabetes and disability was strongest among women 65-69 years old, and diabetes was not associated with disability in women 80 years and older (136). The annual incidence of disability was about 10% among women with diabetes and about 5% among nondiabetics (136). Yet, despite the many studies showing an association between diabetes and poor physical performance, diabetes has also exhibited no association with slow walking speed over four years in the Health and Retirement study of adults 65 years and older (106).

C-reactive protein (CRP)

CRP is a marker of overall inflammation in the body. Although not originally included in the WHO's list of CRFs, inflammatory factors have also been associated with functional status, particularly in the context of "inflammaging" (137). The US Einstein Aging Study suggested that elevated CRP levels were associated with decreased walking speed over two years in adults 70 years and older (138), and the association was stronger in those without vascular diseases. Likewise, in the Health, Aging and Body Composition Study, the relative risk of subsequent mobility limitation associated with per standard deviation increase in CRP was 1.40 (95% CI 1.18-1.68) over 30 months of follow-up (139). These findings remained after exclusion of those with baseline and incident cardiovascular events or hospitalizations. Yet, we also see that CRP is not associated with limitation in mobility over six years in older Italian adults (140). Correspondingly, another study found an association between CRP and disability cross-sectionally, but not longitudinally (141).

Individual vs combined CRFs

Most studies have investigated individual CRFs in association with functional outcomes, however, it is also important to look at the functional impact of their aggregation and severity, as older adults are more likely to experience multiple CRFs concomitantly. The need also to disentangle them helps to understand the specific relationships between each factor and the risk for adverse outcomes, for the development of more precise preventive strategies. Therefore, research that include both clustered and individual CRFs is important. However, very few studies have examined the concomitant effect of multiple CRFs, despite their prominent co-occurrence in older persons, and in relation to a diversity of physical performance measures. A population-based cross-sectional study of older adults in Sweden, using the same population as in this thesis project, showed an increasing linear association between the number of CRFs and an increased likelihood of mobility limitation (142). In the Three City-Study, of adults 65 years and older, an increasing number of unhealthy behaviours (i.e. physical inactivity, low fruit and vegetable consumption, smoking, and alcohol consumption) were associated with a greater risk for disability over 12 years of follow-up. Specifically, participants with three or more unhealthy behaviours had a 2.5-fold higher risk of disability (92).

Some algorithms combining CRFs have been created, such as the Framingham general cardiovascular risk score (FRS) (143). The FRS was developed as part of the Framingham Study for predicting the risk of cardiovascular events and for identifying persons who are at risk, for early intervention (143). The FRS is a well-established risk score for predicting future cardiovascular events and cognitive decline (143,144), however, it has been mainly investigated in middle-aged and younger-old (age <75 years) populations in relation to physical impairment or disability. The English Longitudinal Study of Ageing showed that the FRS can predict frailty in older adults (145), and the Whitehall II cohort study demonstrated an association between trajectories of the FRS change over 16 years according to baseline physical function in a middle-aged population (130). Yet, there is generally a lack of information on the risk among older adult populations.

Table 2. A summary of major longitudinal population-based studies on individual and clustered cardiovascular risk factors and physical function.

Author, Year, Country	Study Population	Follow-up length	Age (years)	Cardiovascular risk factors	Physical function outcome measures	Main findings
Individual cardiovascular risk factors						
Vergheze 2016 USA (106)	Health and Retirement Study N=2306	4 years	65+	Physical inactivity, alcohol, obesity, diabetes, hypertension	Walking speed	Physical inactivity predicted incident slow walking speed (adjusted RR=1.94; 95% CI 1.20-3.12. Alcohol consumption was not associated with incident walking speed limitation. Hypertension did not predict slow walking speed (RR=0.988; 95% CI 0.71-1.39). Obesity predicted slow gait (RR=1.35; 95% CI, 1.07-1.69). Diabetes did not predict slow walking speed (RR=1.16; 95% CI 0.86-1.56)
Sabia 2014 England (104)	Whitehall II study N=5671	17 years	Mean 49.1	Current or recent smoking, nonmoderate alcohol consumption (abstinence or heavy), fruit and vegetable consumption less than twice per day, and physical inactivity	Walking speed	Physical inactivity, alcohol consumption, and smoking were associated with slower walking speed at follow-up.
Koster 2008 USA (94)	Health, Aging and Body Composition study. N=2982	6.5 years	70-79	Physical activity	Mobility limitation (difficulty walking one-quarter of a mile or climbing 10 step)	Low physical activity was associated with future mobility limitation.
Lang 2007 USA & England (95)	The Health and Retirement Study (HRS) N=8702	HRS: Median 72 months (IQR 70–74 months).	50-69	Physical inactivity	HRS: self-reported mobility impairment. difficulty walking several blocks, climbing several flights of stairs, and climbing one flight of stairs	In all BMI categories, those who reported 3 or more days of activity per week had a lower incidence of physical impairment than those who reported less activity
	The English Longitudinal Study of Ageing (ELSA) N=1507	ELSA: Median 73 months (IQR69–77 months).			ELSA: balance, chair stands, and grip strength	
Forrest 2006 USA (93)	Study of Osteoporotic Fractures (SOF) N=5178	10 years	65+	Physical inactivity, smoking, diabetes, hypertension, obesity	Walking speed and chair stand	No association of physical activity with walking speed decline or chair stand decline performance. Higher weight and systolic blood pressure were associated with greater walking speed decline, as well as diabetes and smoking. Higher weight, smoking, and diabetes were associated with decline in chair stand performance. No association between physical activity or alcohol with either physical function.
Wang 2002 USA (107)	Adult Changes in Thought (ACT) Study N=2578	Mean 3.4 years	65+	Diabetes, hypertension, coronary heart disease, cerebrovascular diseases, osteoporosis, arthritis, cancer, low cognitive function,	Walking speed, chair stand, standing balance, and grip strength	Exercise (3 times or more per week) was associated with better physical performance. Smoking was associated with poor physical performance. Alcohol use (5 drinks or more per year without alcohol problems) was associated with better physical performance. Hypertension was associated

				depression, smoking, alcohol use, and exercise		with poor physical performance. Diabetes was associated with poor physical performance.
Rosano 2011 USA (114)	Cardiovascular health study (CHS) N=2733 (724 with MRI)	18 years	65+	Hypertension	Walking speed	Recent hypertension, with uncontrolled blood pressure, and those who successfully controlled blood pressure had an accelerated decline in walking speed.
Dumurgier 2010 France (115)	Three City study N=3604 (1590 did MRI)	Mean 7 years	65-85	Hypertension	Walking speed	People with hypertension had a faster decline in walking speed
Artaud 2016 France (121)	Three city Dijon cohort study N=4007	11 years	65-85	Obesity	Walking speed	Obese persons had a 45% faster walking speed decline.
Stenholm 2010 USA (123)	Health, Aging and Body Composition Study N=2984	6.5 years	70-79	Obesity	Mobility limitation (difficulty walking 1-quarter mile or climbing 10 steps)	Obesity was associated with increased risk for mobility limitation.
Stenholm 2007 Finland (124)	Mini-Finland Follow-up Survey N=840	22 years	32-72	BMI	Walking limitation (<1.2 m/s) or difficulty in walking 0.5 km	High BMI was a predictor of walking limitation.
Launer 1994 USA (122)	NHANES I N=1124	8-16 years (for past BMI) 2-5 (for current BMI)	45-74	BMI and weight change	Mobility disability (walking across a room, climbing two steps, doing heavy chores, carrying a full bag of groceries, running errands, bending to the floor, or transferring from a car, bed, bath chair or toilet)	High BMI was associated with increased risk of mobility disability.
Schalk 2004 The Netherlands (129)	The Longitudinal Aging Study of Amsterdam	3 years	55-85	Serum albumin and total cholesterol	Walking speed and putting on and taking off a cardigan	No association between total cholesterol and functional status in men, but in women low cholesterol associated with decline in function.
Vasunilashorn 2013 Italy (140)	The Invecchiare in Chianti (InCHIANTI) N=1006	6 years	65+	Eight markers of inflammation including C-reactive protein	Walking speed	C-reactive protein was not associated with incident walking limitation. Those with the highest scores of the inflammatory markers showed highest risk of mobility disability.
Vergheze 2012 USA (138)	Einstein Aging Study (EAS) N=624	Median 2 years	70+	C-reactive protein	Walking speed	High C-reactive protein was associated with greater risk of mobility limitation and the association was stronger in those without vascular diseases.
Penninx 2004 USA (139)	Health, Aging and Body Composition Study N=2979	30 months	70-79	C-reactive protein	Difficulty or inability to walk one-quarter of a mile or to climb 10 steps	C-reactive protein was associated with mobility limitation (RR 1.40, 95% CI 1.18-1.68).

Clustered or multiple cardiovascular risk factors

Jin 2017 Italy (131)	InChianti N=906	9 years	65+	Life's Simple Seven score	Short physical performance battery	Cardiovascular health behaviours were protective against poor physical function.
Windham 2017 USA (132)	Atherosclerosis Risk in Communities (ARIC) study N=15 744	25 years	45-64	Life's Simple Seven score	Short physical performance battery	LS7 at mid-life was associated with a better SPPB score in late-life. Ideal glucose, smoking, blood pressure, BMI, and physical activity were most strongly associated with future physical function performance.
Sabia 2014 England (104)	Whitehall II study N=5671	17 years		Current or recent smoking, nonmoderate alcohol consumption, fruit and vegetable consumption less than twice per day, and physical inactivity	Walking speed	All risk factors were associated with a slower walking.
Elbaz 2014 England (130)	Whitehall II cohort study N=5376	16 years	35-55	Framingham general cardiovascular risk score	Walking speed, 5 time chair stand; balance, grip strength, finger tapping	Poor performance on walking speed, chair rises and balance were associated with a higher Framingham general cardiovascular risk score.
LaCroix 1993 USA (105)	Established Populations for Epidemiologic Studies of the Elderly N=6981	4 years	65+	Physical activity, alcohol, smoking, BMI	Intact mobility (the ability to climb up and down stairs and walk a half mile)	Current smoking, consuming alcohol, high BMI, and low physical activity were associated with increased risk of poor mobility.

Reviews and/or meta-analysis of studies investigating various cardiovascular risk factors and physical functions as outcomes: Wong 2013 (diabetes) **(146)**; Bianchi 2016 (diabetes) **(147)**; Vincent 2010 (Obesity) **(120)**.

Life's Simple Seven score includes cardiovascular health factors: smoking, body mass index, physical activity, dietary intake, blood pressure, glucose, cholesterol. Framingham general cardiovascular risk score includes: High-density lipoprotein cholesterol, total cholesterol, systolic blood pressure, cigarette smoking, and diabetes. Short Physical Performance Battery includes: walking speed, chair stand, standing balance.

LS7: Life's Simple Seven; MRI: magnetic resonance imaging; RR: relative risk; CRP: C-reactive protein; BMI: body mass index.

Table 3. A summary of major longitudinal population-based studies on cardiovascular risk factors and disability in activities of daily living.

Author, Year, Country	Study Population	Follow-up length	Age (years)	Cardiovascular risk factors	Disability outcome measures	Main findings
Dhamoon 2017 USA (141)	Northern Manhattan Study N=2240	Median 13 years	40+	C-reactive protein	Barthel index	High C-reactive protein was associated with higher baseline disability, but not with the change of disability over time.
Koye 2017 Australia (126)	The Australian Diabetes, Obesity and Lifestyle (AusDiab) study N=2373	12 years	60+	Diabetes and BMI	ADL	Diabetes was associated with higher odds of disability. BMI and other cardiometabolic factors explained this association.
Artaud 2016 France (121)	Three-City Dijon Study N=4478	11 years	65-85	BMI	Mobility, IADL, ADL	Obese persons had a faster decline in walking speed.
Vu 2016 USA (134)	The Chicago Heart Association Detection Project in Industry N=6014	32 years	Mean 43	Life's Simple Seven score	IADL and ADL	Having a low or moderate risk of CVD at younger age was associated with lower odds of disability in older age.
Artaud 2016 France (121)	Three city Dijon cohort study N=4007	11 years	65-85	BMI	IADL and ADL	Obesity was associated with a higher risk of disability.
Dhamoon 2015 USA (133)	The Northern Manhattan Study -stroke-free N=3219	Median 13 years	40+	Life's Simple Seven score	Barthel Index	Higher cardiovascular health score was associated with higher Barthel Index score.
Artaud 2013 France (92)	Three-City Study N=3982	12 years	65+	Unhealthy behaviors (low/intermediate physical activity, consuming fruit and veggies less than once a day, current smoking/short term ex-smoking, never/former/heavy alcohol drinking)	Mobility, IADL, ADL	Physical activity, low fruit and vegetable consumption, and smoking were associated with increased hazard of disability, but not alcohol intake. Risk increased with the number of unhealthy behaviours.
Chakravarty 2012 USA (97)	University of Pennsylvania alumni N=2327	15.6 years	60+	Low-, medium-, and high-risk based on overweight, smoking, and inactivity	Health Assessment Questionnaire Disability Index (rising, dressing and grooming, hygiene, eating, walking, reach, grip, and routine household activities)	Those with medium and high risk lifestyle factors had a higher risk of disability than the low risk group.
Gerst 2011 Mexico & USA (102)	Mexican Health and Aging Study (MHAS) and the Health and Retirement Study (HRS)	2 years	50+	Vigorous physical activity or exercise	ADL	Physical activity is protective for ADL disability. Those who exercise have a lower probability of transitioning to disability or death.

Liao 2011 Taiwan (98)	Taiwan Longitudinal Study in Aging N=3187	14 years	60+	Not smoking, moderate alcohol consumption, regular exercise, and sleeping 6 to 8 hours per day	ADL (bathing or walking)	Healthy behavior was associated with lower hazard of disability. Increasing number of healthy behaviours showed decreasing likelihood of disability.
Newman 2009 USA (99)	Cardiovascular Health Study (CHS) N=1677	13 years	77-102	Hypertension, physical activity, CVD	ADL	Hypertension and physical inactivity was associated with incident ADL-disability.
Al Snih 2007 USA (127)	Established Populations for Epidemiologic Studies of the Elderly (EPESE) N=12725	7 years	65+	Obesity (BMI $\geq 30\text{kg/m}^2$)	ADL	Subjects with BMI <18.5 or ≥ 30 at baseline were more likely to experience disability during the follow-up period.
Hajjar 2007 USA (116)	Charleston Heart Study N=999	9 years	Mean 68.5	Hypertension $\geq 140/90$ or receiving anti-hypertensive agents	Nagi's Congruency in Medical and Self-Assessment of Disability, the Rosow-Breslaw Scale and Katz's ADL Scale	Greater SBP increase was associated with greater decrease in physical function Hypertensive vs normotensive showed greater decline in function, and a greater risk of developing disability.
Gregg 2002 USA (136)	Women from the Study of Osteoporotic Fractures N=8344	12 years	≥ 65	Diabetes	Walking 0.25 mile, climbing 10 steps, performing household chores, shopping, and cooking meals	Diabetes was associated with a greater risk of any of the limitations.
Wang 2002 USA (107)	Adult Changes in Thought (ACT) Study N=1873	Mean 3.4 years	65+	Diabetes, hypertension, coronary heart disease, cerebrovascular diseases, osteoporosis, arthritis, cancer, low cognitive function, depression, and smoking	IADL and ADL	Diabetes, hypertension, and smoking were associated with more ADL limitation. Alcohol use (5 drinks or more per year without alcohol problems) and exercise (3 times or more per week) was associated with less ADL limitation.
Sarkisian 2000 USA (148)	The Study of Osteoporotic Fractures N=6632	4 years	65+	Benzodiazepine use, depression, low exercise level, low social functioning, body-mass index, poor visual acuity, low bone mineral density	ADL	Low exercise level was a modifiable predictor of functional decline in basic activities, not high BMI.
Pinsky 1985 USA (109)	Framingham Disability Study N=2021	27 years	28-62	Hypertension, diabetes, smoking, BMI, cholesterol	Cumulative disability index	In women, hypertension, BMI, and diabetes were associated with disability; in men, only hypertension was associated with disability. For women current hypertension was associated with disability in the middle and old age groups. Diabetes was associated with disability in the older group, and smoking in the middle age.

Reviews and/or meta-analysis for the outcome of disability: Keysor 2003 (physical activity) **(149)**; Tak 2013 (physical activity) **(96)**; Wong 2013 (diabetes) **(135)**; Samper-Terment 2012 (Obesity) **(125)**.

Life's Simple Seven score includes cardiovascular health factors: smoking, body mass index, physical activity, dietary intake, blood pressure, glucose, cholesterol.

LS7: Life's Simple Seven; FRS: Framingham general cardiovascular risk score; MRI: magnetic resonance imaging; BMI: body mass index; IADL: instrumental activities of daily living; ADL: activities of daily living.

1.5 CEREBRAL SMALL VESSEL DISEASE

Cerebral small vessel disease (SVD) refers to pathological processes affecting the arteries, arterioles, capillaries, and venules of the brain (150,151). The vessels vulnerable to SVD are essential for nourishing the brain and maintaining functioning of its metabolic areas and networks (150). In the past decade, SVD has been increasingly linked to not only clinical stroke, but also cognitive, psychiatric, and physical disabilities. For instance, research has suggested that SVD significantly contributes to cognitive impairment and dementia (152,153), conditions that place a huge impact on economy and society. In addition, evidence has emerged that SVD also plays a role in physical dysfunction, although the majority of current studies have been based on clinical settings (e.g. LADIS) (150,154,155). Despite the importance of SVD on future adverse health outcomes, very few population-based studies have investigated various markers of SVD and their aggregation in association with functional impairment in older people.

Markers of SVD seen on magnetic resonance imaging (MRI) included in this thesis, encompass white matter hyperintensities (WMH), lacunes, and perivascular spaces (PVS).

White matter hyperintensities

WMH appear as hyperintense signals on T2-weighted and FLAIR images on MRI (156). WMH are increasingly common with advancing age and are known to be strongly associated with cognitive impairment, dementia, stroke, decreased mobility, and disability (151,156). They are also associated with the number of CRFs, such as hypertension, diabetes, and smoking (156).

Studies investigating the association between WMH and physical performance in old people, specifically walking speed, are expanding. Many studies have shown consistently an association between greater WMH volume and increased risk of walking speed limitation (153,157-160), both cross-sectionally and longitudinally (**see Appendix table 1 for cross-sectional studies that are not included in the reviews**). For example, it was demonstrated in a sample from the Oregon Brain Aging Study that higher total WMH volume was associated with an increased rate of decline in walking speed over 13 years in adults 65 years and older (161). It is assumed that WMH could interfere with motor and sensory tracts that are paramount for performing gait and balance. Research has suggested that subtle brain abnormalities can be observed in physical performance, even in high-functioning older adults (162). However, longitudinal studies in older adult populations are needed to understand this association.

It has also been suggested that SVD is on the pathway between CRF and the decline in physical function. Hypertension has been most often examined in association with WMH, however, the potential role of WMH remains unclear. In the Three-City Study including adults 65-89 years of age, they found that the association between hypertension and walking speed decline was partly mediated by white matter lesions and lacunar infarcts (115). However, the longitudinal Cardiovascular Health Study found that WMH were not an intermediate factor in the association between hypertension and walking speed decline in older adults (114).

Lacunes and perivascular spaces

Lacunes are defined as cerebral spinal fluid-filled cavities, and are often considered to be asymptomatic (150). So far lacunes have not been studied often in regards to physical function or disability. Some population-based cross-sectional studies showed no association of lacunes with walking speed performance (**See appendix table 1**), whereas longitudinally, it has only been investigated in a clinical setting of a stroke population (163).

Perivascular spaces (PVS) are potentially enlarged compartments around blood vessels that run through the subarachnoid space and penetrate the brain parenchyma, and act as passages for carrying solutes and for lymphatic drainage (151,164). Population-based studies have shown that PVS are more frequent in older adults in the presence of hypertension and in those with carotid atherosclerotic plaques (165), and are correlated with other markers of SVD, such as WMH and subcortical infarcts (166,167), suggesting that PVS are a marker of SVD. Similar to WMH, PVS have been examined in relation to physical status only in very few studies, either cross-sectionally (168,169) or longitudinally in patient samples (167,170). One longitudinal study of 259 stroke patients found no association between PVS and functional limitation after three months (170), however, another longitudinal study in acute stroke patients PVS were associated with future mobility limitation after three years, but mobility was assessed according to self-reports (167). Longitudinal data from general population settings are lacking.

SVD burden

Despite all the various SVD being of vascular origin, they inherently contain slightly different etiopathophysiological features. Thus, it is also important to examine the combined or cumulative effect of these hallmarks of SVD on physical function, as the whole spectrum can provide a measure regarding the global burden (e.g. severity and intensity) of SVD damage in the brain. However, although an important topic, little is known regarding the functional phenotypes or consequences of cerebral load of SVD, and is only gaining interest recently (171). Global SVD burden has been examined in a normal aging population cross-sectionally (168), demonstrating an association with physical limitation, whereas longitudinally it has been mainly examined in stroke populations with conflicting results (163,170). This emphasizes the need for more population-based studies to better understand the relationships of individual markers and the global burden of SVD and physical function longitudinally in healthy older adults.

1.6 KNOWLEDGE GAP

A void of understanding persists regarding CRFs and biological and vascular pathways leading to late-life physical limitation and disability. First, it is well-established that walking speed is associated with increased risk of various adverse events, but its relationship with other mobility measures and the extent of its predictive power for disability in isolation and joined with other mobility limitations among older adults remains unclear. Second, earlier studies have focused on individual CRFs in association with physical limitation and disability, however, these CRFs often occur concurrently among older adults and may exert an accumulative effect on physical limitation and their progression, but this remains sparsely examined. Third, most studies have examined the association between CRFs and only walking speed, disregarding other physical function tests, which can provide us with more information. Finally, few population-based studies have investigated the pathophysiological mechanisms linking CRFs with deterioration in physical function in aging. Markers of SVD have been previously studied mostly in relation to cognitive outcomes, however, there is a lack of investigation into their association with physical function, especially longitudinally, except for WMH. Particularly, the role of lacunes, PVS, and the important role of the global burden of SVD on incipient physical function remains predominantly under-studied.

In addition, earlier research has convinced us that disability has a tremendous negative impact on older persons and society and CRFs and physical performance are areas of intervention. Yet, studies have repeatedly been performed in middle-age populations to predict late-life consequences. There is a paucity of investigation into older population-based cohorts. Further, there is a lack of comparison between the younger-old and older-old. It is established that starting early is beneficial, but is it ever too late and which factors are most important?

Moreover, studies investigating the risk of physical limitation or disability have not been performed in relatively healthy samples (e.g. free of physical limitation and CVD). Comprehension into the functional consequences of CRFs among older adults with good physical function and free of CVD can provide crucial information in developing useful tools for early intervention to postpone or even prevent the occurrence of the adverse events.

2 AIMS

HYPOTHESIS

We hypothesized that CVD-related risk factors and their aggregation play a crucial role in the atherosclerotic process in the absence of CVD, increasing the risk of physical limitation and inducing the progression to disability, even among older adults. Yet, differences may exist in regards to older age cohorts. Also, potential biological pathways leading to the progressive decline in physical limitation, may be through brain abnormalities of vascular etiology.

GENERAL AIM

The overall aim of this doctoral project is to investigate the role and potential neuropathological mechanisms of cardiovascular risk factors in the development of physical limitation and disability in older adults.

SPECIFIC AIMS

Specific aims will be addressed in a series of four individual studies, as specified below:

Study I. To estimate the risk of developing disability in activities of daily living (ADL) according to limitations in walking speed, balance, or both in older adults. Further, to explore the role of chronic diseases and cognitive function in this association.

Study II. To examine the association of the cardiovascular risk burden with the development of physical limitation in the younger-old (60-72 years old) and older-old (≥ 78 years) adults.

Study III. To examine whether cardiovascular risk factors are associated with increased risk of disability, and to verify the role of functional limitation and age in this association.

Study IV. To explore whether, and to what extent, imaging markers of cerebral microvascular pathologies are associated with incipient physical limitation in older adults.

3 MATERIALS AND METHODS

3.1 SWEDISH NATIONAL STUDY ON AGING AND CARE IN KUNGSHOLMEN (SNAC-K) POPULATION STUDY



General description

The population-based Swedish National study on Aging and Care in Kungsholmen (SNAC-K) is an ongoing, longitudinal study undertaken in the urban district of Kungsholmen, Stockholm, Sweden, by the Stockholm Gerontology Research Center in collaboration with the Aging Research Center, Karolinska Institutet and Stockholm University (172). The purpose of SNAC-K is to investigate and increase comprehension into the aging process and health of the general older population in central Stockholm for the development of preventative strategies. SNAC-K is one of four longitudinal studies, as part of a national multi-center study called SNAC taking place in other regions of Sweden (<http://www.snac-k.se/>).

Study population

All the data for this doctoral project are derived from SNAC-K. The SNAC-K participants consist of a random sample of older adults, aged 60 years and older, living in their homes or in institutions on Kungsholmen. They were recruited between March 2001 and June 2004, at baseline, the sample was stratified into eleven age cohorts, with six year intervals between the younger cohorts (60, 66, and 72 years old), and a three year intervals between the older cohorts (78, 81, 84, 87, 90, 93, 96, and 99 years and above). This method was undertaken due to more rapid changes and higher attrition rates among older adults. Follow-up data were collected

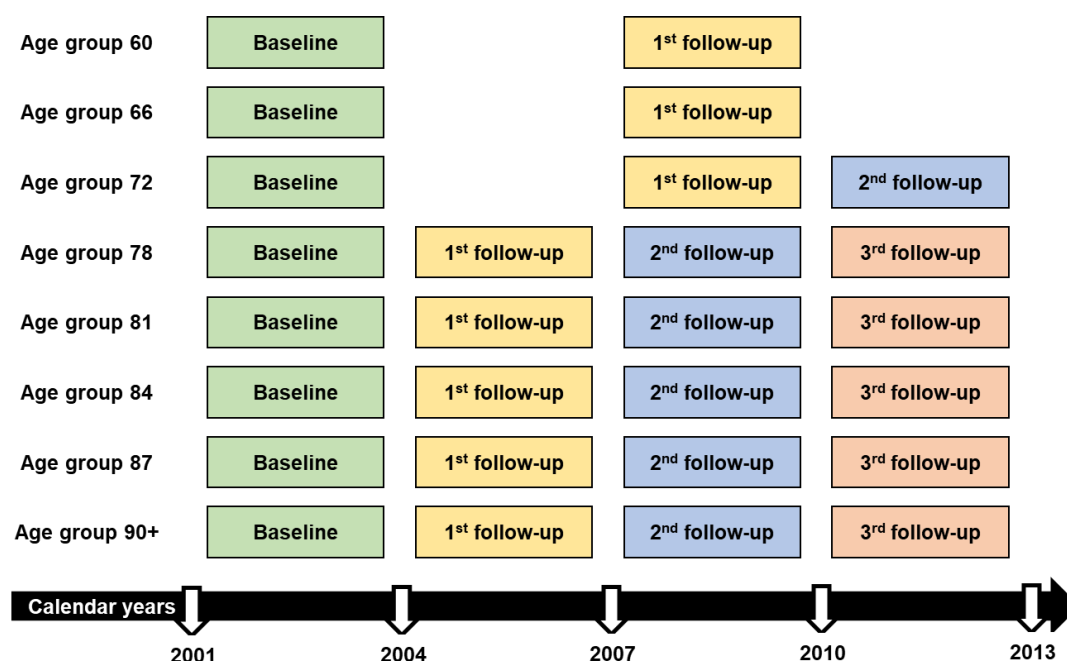


Figure 3. Swedish National study on Aging and Care in Kungsholmen cohorts, 2001-2013.

every six years for the younger age cohorts and every three years for the older-old age cohorts (**Figure 3**). By the year 2013, the first follow-up for young-old cohorts and the third follow-up for the older cohorts had been completed for SNAC-K. Of the 5111 persons initially invited, 321 were ineligible and 200 died, leaving 4590 alive and eligible, of which 1227 (1227/4590, 27%) declined before being called for the examination, leaving a sample of 3363 (73.3%) persons to participate at the baseline examination (**Figure 4**). For those unable to come to the research center (n=717), home visits were performed.

In September 2001 to October 2003, a random sub-sample of noninstitutionalized, nondisabled, and nondemented SNAC-K participants across all age strata (n=555) were invited and agreed to have brain MRI scans. Only the fourth study of the doctoral project was based on the SNAC-K MRI dataset.

Age groups (year)	Random sample		Alive & eligible		Examined
60	1095		978		739
66	780		730		565
72	707	321 ineligible 200 died	652	1227 declined	478
78	700		642		461
81	369		335		236
84	346		316		224
87	304		260		174
90+	810		677		486
Total	5111		4590		3363

Figure 4. SNAC-K study population flowchart, by age group, from the baseline (2001-2004) initial random sample to the alive and eligible sample, and then the final examined sample, after excluding those who were ineligible, died, or declined.

3.1.1 Study samples

Study samples for this thesis were derived from SNAC-K baseline, 3-year (April 2004 to June 2007), 6-year (July 2007 to October 2010), and 9-year (March 2010 to February 2013) follow-up surveys. The SNAC-K MRI sub-sample was used for Study IV. **Figure 5** shows the flowchart of participants for the four studies in this thesis.

All the studies were longitudinal in study design. Study I included a total of 1971 participants, study II was composed of 3 sub-samples of 1441, 1154, and 1496 participants free of limitation in walking speed, balance stand, and chair stand, respectively, and CVD. Study III included 1756 disability- and CVD-free participants at baseline, and 331 persons free of walking speed limitation in study IV. Study I used data up until 2010, while the other three studies used data until 2013.

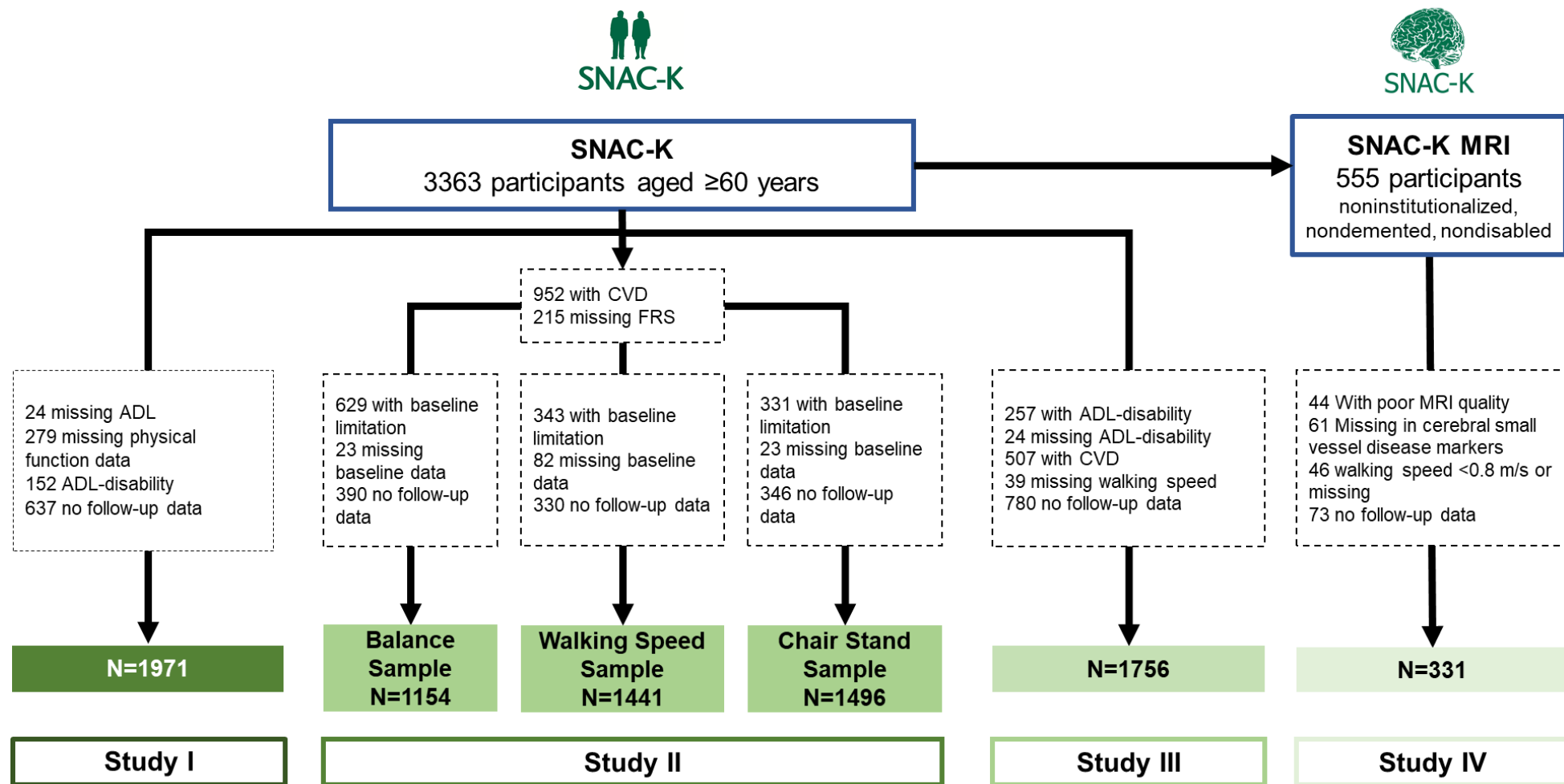


Figure 5. SNAC-K Project and SNAC-K MRI study population flowchart. Figures illustrates number of persons at baseline, those excluded from the analyses (in perforated boxes), and the final analytical samples for studies I to IV.

3.2 DATA COLLECTION AND DEFINITIONS

Data on demographics (age, sex, and education), physical functional status (e.g. walking speed, balance, chair stand, and ADL), global cognitive function (e.g. Mini-Mental State Examination [MMSE]), medical history, CRFs (e.g. smoking, hypertension, diabetes, obesity, and heavy alcohol consumption), and CVDs (e.g. coronary heart disease and cerebrovascular diseases), and current use of medications (e.g. antihypertensive, blood glucose-lowering agents) were collected at baseline and each follow-up, by physicians, nurses, and psychologists in accordance with standard protocols (available at <http://www.snac-k.se/>), which took about six hours to perform. Information was also gathered from Swedish National Patient Register and laboratory tests. Peripheral blood samples were taken, and glycated hemoglobin, serum total cholesterol, and genetic polymorphisms were determined following standard procedures.

Cardiovascular risk factors

Physical activity was assessed through the self-administered questionnaire asking how often light physical activity (e.g. walks on the street and parks, short bike rides, light gymnastics, golf) and high intensity physical activity (e.g. jogging, brisk long walks, heavy garden work, long bike rides, intensive gymnastics, long distance skating, skiing, swimming, ball sports) was performed in the last 12 months. This question was then dichotomized into active (weekly participation in physical activity of moderate-to-vigorous intensity) and inactive (less than weekly participation in physical activity of moderate-to-vigorous intensity), according to current recommendations (88,173). **Alcohol consumption** was assessed based on frequency and amount consumed on a typical drinking day, and was classified as none or occasional, light to moderate (1-4 drinks per week for men and 1-7 drinks/week for women), or heavy (>14 drinks/week for men or >7 drinks/week for women) (174). **Smoking status** was recorded in study II as current or not current and as never or ever (current or former) in study III and IV. **Seated arterial blood pressure** was measured twice on the left upper arm with a sphygmomanometer, and the mean value was used for the analysis. **Systolic blood pressure (SBP)** was used as a continuous variable (Study II) or categorized into four groups (Studies III and IV), slightly modified from a previous study (175) (<130, 130-139, 140-149, and ≥ 150 mmHg) and **diastolic blood pressure (DBP)** in four categories (<70, 70-79, 80-89, and ≥ 90 mmHg). **Use of anti-hypertensive agents** were classified according to the Anatomical Therapeutic Chemical classification system (ATC codes: C02, C03, and C07-C09). **High total cholesterol** was defined as a nonfasting level of ≥ 6.22 mmol/l or use of cholesterol lowering agents (ATC code C10). **Diabetes** was defined according to self-reported history, records from the National Patient Register, the use of hypoglycemic agents, or $\geq 6.5\%$ glycated hemoglobin level (176). **BMI** was determined according to weight in kilograms divided by the square of the height in meters and categorized as underweight (<20 kg/m²), normal (20-24.9), overweight (25-29.9), and obese (≥ 30). **CRP** is a common measure of overall inflammation level of the body. Serum CRP was measured following standard protocols, and high CRP was defined as serum level ≥ 5 mg/L (177).

CRF burden

Burden of CRFs was assessed using the **Framingham general cardiovascular risk score (FRS)** (143). The FRS includes: age, sex, systolic blood pressure, antihypertensive treatment, total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking, and diabetes. However, we did not include HDL-cholesterol in our FRS algorithm, due to lack of data. The factors are sex-weighted and the total score is determined by summing all the factors together. A higher score indicates greater risk of a future cardiovascular event.

Magnetic resonance imaging acquisition and measurements

MRI protocol

Participants were scanned on an Intera 1.5T scanner (Philips Healthcare, Best, the Netherlands). The protocol included an axial three-dimensional T1-weighted fast field echo (repetition time [TR] 15 ms, echo time [TE] 7 ms, flip angle [FA] 15°, field of view [FOV] 240, 128 slices with slice thickness 1.5 mm and in-plane resolution 0.94×0.94 mm, no gap, matrix 256×256); an axial turbo fluid-attenuated inversion recovery (FLAIR, TR 6000 ms, TE 100 ms, inversion time 1900 ms, FA 90°, echo train length 21, FOV 230, 22 slices with slice thickness 5 mm and in-plane resolution 0.90×0.90 mm, gap 1 mm, matrix 256×256); and a proton-density/T2-weighted (TR, 3995 ms; TE, 18/90 ms; echo-train length, 6; flip angle, 90°, 60 3-mm sequential images without a gap or angulation) sequence (178).

MRI markers of cerebral small vessel disease

WMH were manually delineated on the FLAIR images by a single rater (Grégoria Kalpouzos), and further interpolated on the corresponding T1-weighted images to compensate for the gap between slices in FLAIR. Intra-rater reliability was assessed with Dice coefficient, which was equal to 0.76 (SD 0.09) (for details, see Köhncke et al. 2016 (179)). WMH volume was adjusted for total tissue volume.

Lacunes were defined as small lesions with cerebrospinal fluid signal on all sequences and surrounding high signals on FLAIR sequences. PVS were assessed using a visual rating scale (178). T1 and T2 images were used to assess PVS in different brain areas (e.g. frontal lobe, parieto-occipital lobe, basal ganglia, thalami) in each hemisphere. The number of PVS was scored in each region from 0-3: 0 (no visible PVS), 1 (1-5 PVS), 2 (6-10 PVS), or 3 (>10 PVS). Scores were then summed to a maximum of 24. All PVS assessments were undertaken by a clinical neuroradiologist (Anna Laveskog). Six months after, 20 randomly selected participants were rerated for PVS, demonstrating an excellent intra- and inter-rater reliability (both weighted $\kappa=0.77$).

Cerebral SVD burden was evaluated using a score that included WMH, PVS, and lacunes, categorizing each into a dichotomous variable with values of either 0 or 1. A score of 1 was given to those who were categorized in the top tertile of WMH volume, in the top tertile of number of PVS, or had lacunes present. The value for each of the three SVD markers were then summed to create a SVD burden, ranging from 0 to 3.

Physical limitations and disability

Physical performance measures included the one-leg balance stand, walking speed, and five times sit-to-stand chair stand tests, assessed by the nurse at baseline and follow-ups. Disability was defined according to basic activities of daily living (ADL) at baseline and follow-ups.

One-leg balance stand was measured, asking the participant, without shoes, to stand as long as possible, up to 60 seconds, first on one leg then the other. Testing stopped if the participant's foot touched the floor, if their bent foot was supported on the standing leg, if the standing foot's position changed, if they lost balance, or reached the maximum time of 60 seconds. If they reached the maximum time on the first try, the second attempt was not pursued on that leg. Otherwise, each leg was tested twice and the best overall score was used. Balance limitation was defined as the common cut-off of < 5 seconds (67,180,181).

Walking speed was assessed by asking the participants to walk for 2.44 or 6 meters. The distance was based on the participant's self-rated usual speed. Self-rated fast or normal walkers completed the longer distance, whereas self-rated slow or very slow walkers performed the shorter walk. At home visits, the shorter walk was always performed, because of limited space. Walking speed is the time from whichever length was walked in the analyses, and is presented in meters per second (m/s). For participants who were unable to walk, a value of 0 m/s was recorded. The participants had a 2 m flying start before timing, to measure a consistent pace. Participants used their usual walking aids during the test. Walking speed limitation was defined according to the commonly used cut-off of a usual walking pace < 0.8 m/s (40,43,182).

Chair stand was tested by asking the participants to fold their arms across their chests and to stand up from a sitting position once. If participants successfully rose from the chair, they were asked to stand up and sit down five times as quickly as possible. The time required to complete the task was measured in seconds (46). Chair stand limitation was defined as the inability to stand up from the chair.

Dependence in basic **ADL** (i.e. bathing, dressing, toileting, transferring from bed to chair or in and out of bed, and feeding) was evaluated by counting the number of activities with which the subjects needed help. Disability was defined as the inability to undertake 1 or more ADL.

Additional variables

Confounding is one of the biases common in observational studies. Confounders were defined as variables that are associated with both the exposure and the outcome, however, not on the causal pathway. That is, the confounder is a risk factor for the outcome, and is associated with the exposure, but is not a result of the exposure (183).

Global cognitive function was assessed using the Mini-Mental State Examination (MMSE) (184). DNA was extracted from peripheral blood samples using standard methods. Genotyping was performed using MALDI-TOF (Matrix Adsorbed Laser Desorption-Ionisation-Time Of Flight) analysis on the Sequenom MassARRAY platform at the Mutation Analysis Facility, Karolinska Institutet as described elsewhere (185,186), with minor modifications. For the current project *APOE* gene was analyzed and dichotomized as $\epsilon 4$ carriers vs. noncarriers.

Information on health history for all participants was also available from the Swedish National Patient Register where all in-patient care and specialized outpatient care services in Sweden since 1969 are recorded and can be linked to the SNAC-K database. Date of death was obtained from the Swedish Cause of Death Register. For health status criteria of the ninth and tenth revisions of the International Statistical Classification of Diseases and Related Health Problems (ICD-9 and ICD-10) were used. History of CVDs was ascertained by integrating data from clinical examination, electrocardiogram, and medication use collected during the study visit and information from the Swedish National Patient Register (187). We included four major CVDs, i.e., coronary heart disease (ICD-9 codes 410-414; ICD-10 codes I20-I25), heart failure (ICD-9 code 428; ICD-10 code I50), atrial fibrillation (ICD-9 code 427.8; ICD-10 code I48), and cerebrovascular disease (ICD-9 codes 430-438; ICD-10 codes I60-I69). Medical drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system (ATC codes C02, C03, C07-C09) (188).

3.3 STATISTICAL ANALYSES

Statistical software Stata[®], version 14 or 15 (StataCorp, College Station, Texas, U.S.A.) for Windows, was used to perform all statistical analyses. **Table 4** displays the outcome variables, predictors, potential confounders, and methods of statistical analyses for all four studies of the thesis.

For basic and descriptive statistics, Student T tests, χ^2 tests, and ANOVA were employed to compare means of two groups of normal distributed continuous variables, when comparing two or more groups of categorical variables, and when the comparisons are more than two groups, respectively. Mann-Whitney U-test was used for skewed data.

Prevalence of limitation in walking speed and balance, and ADL-disability at baseline stratified by age was estimated and incidence rates (events per 100 person-years) over the follow-ups were calculated (Study I).

Binary logistic regression was used to estimate the odds ratio (OR) of ADL-disability associated with baseline mobility limitation (Study I) while taking into account follow-up time. In studies II, III, and IV Cox proportional hazards models were constructed to estimate hazard ratios (HR) and 95% confidence intervals (CI) for incident physical function limitations (Study II), incident ADL-disability (Study III), and incident walking speed limitation (Study IV) using follow-up time as the time scale, in relation to baseline FRS (Study II), CRFs (Study III), and markers of cerebral SVD (Study IV). Events were censored at first occurrence, otherwise censoring occurred at the end of the follow-up, or when participants died or dropped-out if the event did not occur. In studies II and III all analyses were stratified by age (60-72 and ≥ 78 years) owing to potential interaction with age. All Cox analyses met the assumptions of proportionality.

Linear mixed-effects models were also employed to examine average annual change in walking speed as a continuous variable in relation to baseline FRS quartiles and markers of cerebral SVD, in studies II and IV, respectively. Each linear mixed-effect models included a predictor, follow-up time, and an interaction term between the predictor and follow-up time. In study II models, age, sex, education, other lifestyle factors (BMI, physical inactivity, alcohol

consumption), CRP, and MMSE score were adjusted for. Models in study IV were adjusted for age, sex, education, CRFs, MMSE, CRP, *APOE* $\epsilon 4$ status, chronic diseases, and CVDs.

Multinomial logistic regression was utilized when the outcome was multiple levels to assess also death as an outcome (Study I), otherwise competing risk analysis with Cox models was performed to take death into account (Studies II, III, and IV).

Population attributable risk (PAR) estimates the proportion of new cases that would not occur if a particular risk factor was absent. PAR was calculated in study III using `punafcc` command in Stata after running the Cox models for CRFs that were significantly associated with ADL-disability. It provides a useful quantitative estimate of potential effect of interventions to reduce or eradicate the risk factor.

Statistical interactions were examined for chronic diseases and cognitive function with mobility limitations at baseline for incident ADL-disability (Study I), sex and FRS for various physical function limitations (Study II), CRFs and walking speed or sex (Study III), and markers of SVD and sex, age, or *APOE* $\epsilon 4$ status (Study IV), using a cross-product term, and considered to have potential statistical interactions at a *P* level <0.10. Joint effects were calculated in study I for baseline balance and walking speed limitation on incident ADL-disability, and in study III for combined baseline physical activity and walking speed status on future ADL-disability.

Inevitably, in epidemiological studies missing data will occur. Missing data in the predictors can potentially lead to bias in the risk estimates and loss of statistical power. Two different methods of handling missing data were utilized in this thesis: dummy variable approach and multiple imputation by chained equation (189). Dummy variable method helps maintain statistical power, however, is only used with few missing data < 5%. Otherwise multiple imputation has been suggested as a valid and more appropriate method of filling in missing values and helping to maintain good statistical power. Missings were considered using the dummy variable approach for sensitivity analyses in studies I, II, and IV. Multiple imputation was undertaken in study III because 11% of the population was missing due to missing data in covariates.

Time-varying covariates were also considered in Cox models for study II for MMSE and CVD.

Table 4. Outcomes, predictors, potential confounders, and main statistical analysis approaches used in the four studies included in the thesis.

Study	Outcome	Predictors	Potential confounders	Statistical analyses
Study I	ADL-disability	Balance and walking speed limitation	Age, sex, and education, CRFs, MMSE score, chronic diseases	Logistic regression models
Study II	Walking speed, balance, and chair stand limitation	Individual CRFs and FRS	Age, sex, and education, other lifestyle factors not included in the FRS (BMI, physical inactivity, alcohol consumption), CRP, MMSE score	Cox models Linear mixed-effects models
Study III	ADL-disability	Individual CRFs	Age, sex, education, mutual CRFs, antihypertensive drug use, DBP, MMSE score, <i>APOE</i> $\epsilon 4$, chronic diseases	Cox models PAR
Study IV	Walking speed	WMH, lacunes, PVS, SVD burden	Age, sex, education, CRFs, MMSE score, CRP, <i>APOE</i> $\epsilon 4$, number of chronic diseases, CVDs	Cox models Linear mixed-effects models

ADL: activities of daily living; CRFs: cardiovascular risk factors; FRS: Framingham general cardiovascular risk score; CRP: C-reactive protein; MMSE: Mini-Mental State Examination; WMH: white matter hyperintensities; PVS: perivascular spaces; SVD: cerebral small vessel disease; BMI: body mass index; DBP: diastolic blood pressure; *APOE*: Apolipoprotein E gene; PAR: population attributable risk; CVD: cardiovascular disease.

3.4 ETHICAL CONSIDERATIONS

The two major ethical concerns in regards to data collection for the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) are informed consent and anonymity.

Contacting the participants for SNAC-K involves multiple steps. First, participants are informed in writing and verbally. Initially, a personal letter is sent two weeks before the visit to explain the purpose, duration, and what is entailed in the study, and the role and importance of the participant. It is clearly stated that it is voluntary, and that they may discontinue at any time without expressing why. Then, a nurse calls the participants directly to confirm their participation in the study in order to set an interview time, followed by a letter being sent confirming the date and time of the interview. In the case of the participant being cognitively impaired, the participant and a proxy (family member or caregiver) are asked to give consent. Both oral and written consent to participate is given by the participants. The participants are also asked whether they wish to be informed of disease status in the event of detection. If such a case occurs, their family doctor will be informed. Also, upon request reports on laboratory tests may be provided. The study follows the ethical principles described in the humanistic-Samhällsvetenskapliga Forskningsrådet, in Sweden, in line with those expressed in the Declaration of Helsinki.

During the examination to establish trust and comfort, assessments occur in a friendly and comfortable environment with sufficient time allocated. All tests were created to minimize discomfort of the participants during the examination. Considerations are also made in regards to the safety of the participants, for example, when performing the one-leg balance stand test. Nurses are nearby and assess if there is a risk of falling or injury, therefore they avoid the participant performing risky tests that can compromise their health. If at any time during the examination anguish or discomfort is expressed, the interview will be immediately terminated, regardless of whether the person or proxy has previously given consent. Feedback is provided to all participants regarding the progression and results of the research, either through seminars, brief reports, or popular scientific articles.

At the SNAC-K center completed questionnaires are stored in locked drawers. The database group enter and save the data into the database system following the rules for security and privacy. Permission must be granted by the principal investigator of the SNAC-K study in order for researchers to utilize the data. Selected data that are distributed for research is only marked with a code, anonymizing the participants name and personal identification (personnummer). All researchers in SNAC-K follow the guidelines, as well all research in SNAC-K follows the principles established in the Declaration of Helsinki.

SNAC-K received ethical permission for baseline and follow-ups of 3-, 6-, and 9- years (SNAC-K: Dnrs 01-114, 04-929/3, 2007/279-31, Ö 26-2007, 2009/595-32; 2010/447-31/2), as well as for the use of the Swedish Patient Register that covers all hospitalizations since 1969 in Sweden and death certification (Dnr: 2009/595-32) from the Regional Ethics Review Board in Stockholm.

4 MAIN RESULTS

Below are the main results from each of the individual studies in the thesis. For more details, see the published papers and manuscripts at the end of the thesis.

4.1 MOBILITY LIMITATION AND FUTURE DISABILITY (STUDY I)

At baseline of the 3060 persons, 5.0% had disability in activities of daily living (ADL), which was more apparent in those ≥ 78 years old than those < 78 . **Figure 6** shows the age-specific prevalence of balance, walking speed limitation, and ADL-disability.

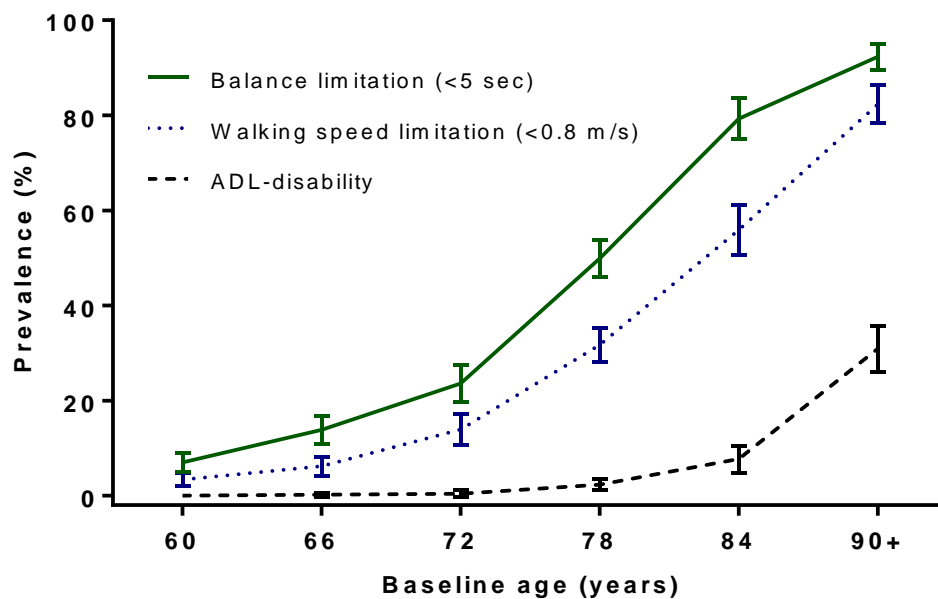


Figure 6. Prevalence per 100 of balance and walking speed limitation, and ADL-disability by age at baseline (n=3060).

Prevalence of limitation was highest for the one-leg balance stand test, followed by walking speed limitation and ADL-disability across all age groups. Of note, the prevalence of disability increased tremendously after age 84 years (dashed black line in Figure 6).

In the incidence analysis (n=1971, reported in figure 6), 119 (6.0%) persons developed ADL-disability during the six years of follow-up, with an incidence rate of 1.5 per 100 person-years. Incidence rates for ADL-disability were higher for those with walking speed limitation than those with only balance limitation across all age groups.

Having limitation in either balance or walking speed at baseline was associated with a greater likelihood of developing incident ADL-disability after six years of follow-up, even in the fully-adjusted model, controlling for age, sex, education, baseline MMSE, and chronic diseases. The associations of physical limitation with ADL-disability were higher in those < 78 years of age than ≥ 78 years of age. However, the changes in results from the demographic-adjusted model (age, sex, education) to the fully-adjusted model showed a greater attenuation in the estimates

in those who were ≥ 78 years of age than those < 78 years of age. Also, there was a linear trend towards a decreasing balance or slowed walking speed over time being associated with a greater risk of disability ($P < .001$).

Additionally, a joint effect was observed, where persons having limitations in both balance and walking speed simultaneously displayed the greatest risk of ADL-disability, than those having only balance limitation or only walking speed limitation (**Figure 7**). Results remained similar when death was taken into account.

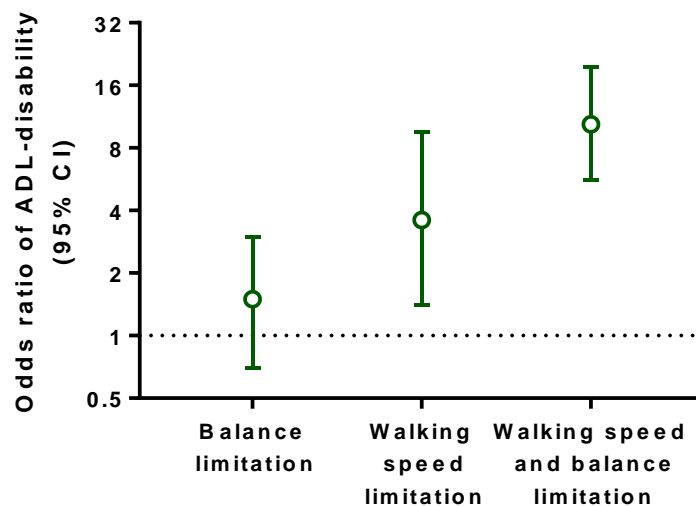


Figure 7. Association between individually and combined limitation in balance and walking speed and incident ADL-disability ($n=1971$), adjusted for age, sex, education, follow-up time, chronic diseases, and MMSE score over six years. CI: confidence interval; ADL: activities of daily living.

4.2 CRF BURDEN AND FUTURE PHYSICAL LIMITATION (STUDY II)

In the analytical samples who were free of CVD and physical function limitation (walking speed $n=1441$; balance $n=1154$; chair stand $n=1496$), a heavier cardiovascular risk burden, defined according to the Framingham general cardiovascular risk score (FRS) was associated with increased risk of walking speed limitation (adjusted Hazard Ratio [aHR] 1.09, 95% confidence interval [CI] 1.02–1.17) in adults < 78 years old, but not in those ≥ 78 years old (aHR 0.98, 95% CI 0.92–1.03) over nine years of follow-up. The association between CRF burden and walking speed limitation was only evident in those 60–72 years of age. This association was still present after controlling for other lifestyle factors (physical inactivity, alcohol consumption, BMI), CRP, and MMSE score at baseline. Furthermore, there was a faster average annual decline in walking speed in those with the highest CRF burden compared to those with the lowest burden (**Figure 8**). There was an association observed between CRF burden and risk of balance limitation in the demographic-adjusted model in only adults < 78 , but this association became non-significant in the fully-adjusted model. There was no significant association found between the FRS and chair stand limitation.

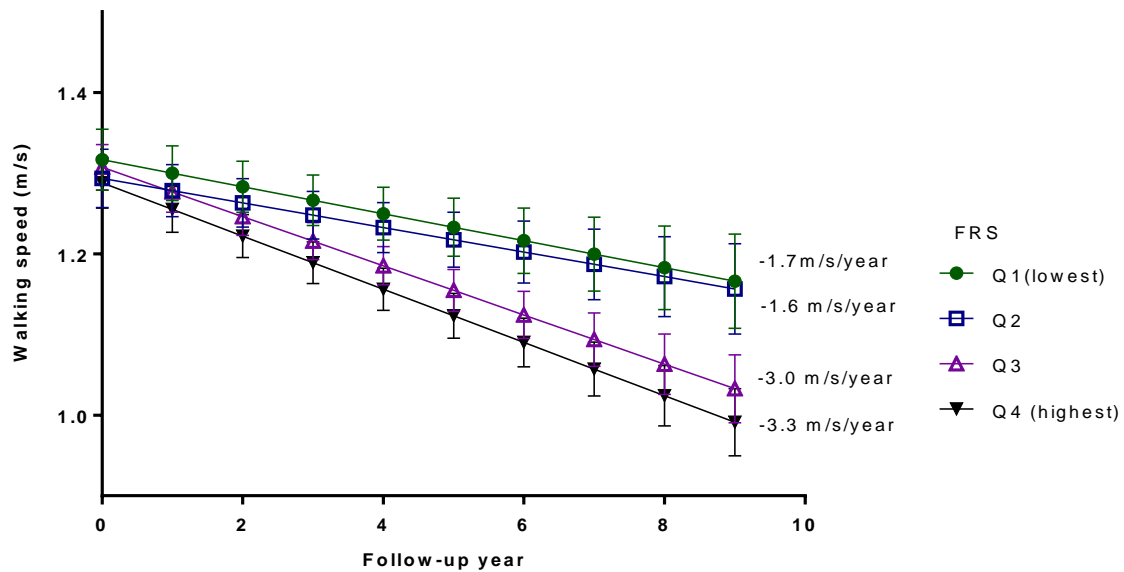


Figure 8. Average annual decline in walking speed according to burden of cardiovascular risk factors defined by the Framingham general cardiovascular risk score (FRS) in adults 60-72 years old, controlling for age, sex, education, other lifestyle factors, C-reactive protein, and Mini-Mental Examination score.

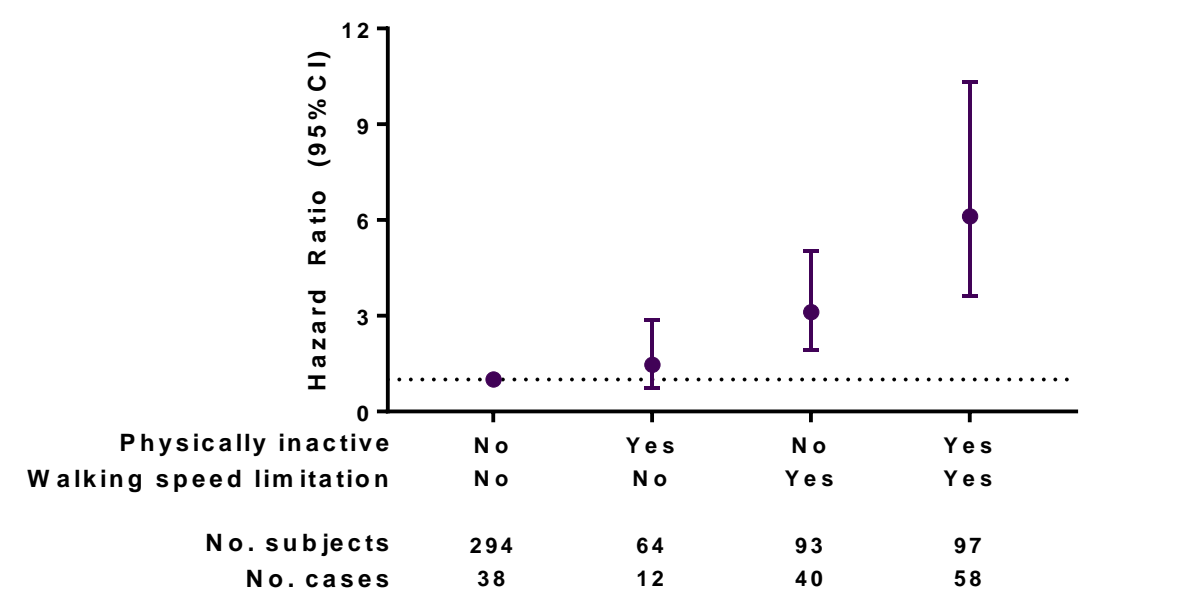
When the CRFs were examined individually in association with the various physical functions, in the younger-old adults (60-72 years old), physical inactivity, current smoking, diabetes, and obesity showed a strong association with future walking speed limitation. For balance limitation an association only occurred with being underweight, and for limitation in chair stand there were significant associations with diabetes, current smoking, underweight, obese, and physical inactivity. These associations persisted after taking death occurring during the follow-up periods into account.

4.3 CRFS AND FUTURE DISABILITY (STUDY III)

In the analytical sample free of CVD and ADL-disability, among the younger-old (60-72 years old) physical inactivity (aHR 4.10, 95% CI 1.22-13.76), diabetes (aHR 5.61, 95% CI 1.17-26.82), and high CRP (aHR 95% 2.78, 95% CI 1.07 -7.22) were significantly related with a greater risk of disability in ADL after nine years of follow-up, even after adjusting for age, sex, education, mutual CRFs, anti-hypertensive drug use, DBP, *APOE* $\epsilon 4$ status, MMSE score, and chronic diseases. There were no significant associations with other CRFs (alcohol consumption, smoking, hypertension, high total cholesterol, obesity). Among the older-old (≥ 78 years old) only physical inactivity was associated with a higher likelihood of incident ADL-disability (aHR 1.99, 95% CI 1.36-2.93).

There was a significant interaction observed between physical activity and walking speed at baseline only in the older-old cohorts, such that being physically inactive and having walking speed limitation concomitantly, showed an even higher risk of ADL-disability (**Figure 9**). However, no interaction was observed between any other CRFs and walking speed limitation, and no interactions in the young-old cohorts. Eliminating physical inactivity would decrease

the proportion of people with disability by 42.7% as calculated by the population attributable risk. Only after taking death into account the association between CRP and incident disability



become significant, otherwise all other associations remained.

Figure 9. Hazard ratio (95% confidence interval [CI]) for the association between baseline physical activity and incident ADL-disability by walking speed limitation status in adults 78 years and older (n=548), controlling for age, sex, education, mutual cardiovascular risk factors, anti-hypertensive drug use, diastolic blood pressure, *APOE* ε4, Mini-Mental State Examination score, and chronic diseases.

4.4 CEREBRAL SMALL VESSEL DISEASE AND WALKING SPEED DECLINE (STUDY IV)

In the walking speed limitation-free MRI-sample of SNAC-K, at baseline, there was a faster average annual decline in walking speed in older adults with one (multiple-adjusted β coefficient -0.017, 95% CI -0.03, -0.004) or two or three SVD simultaneously (β -0.019, 95% CI -0.04, 0.001), compared to none. When examining individual markers of SVD, this association with walking speed decline was only significant for WMH β -0.020; 95% CI -0.035, -0.004) (**Figure 10**).

Over the follow-up, 76 persons (23.0%) developed walking speed limitation. Of the three markers of SVD (WMH, PVS, presence of lacunes), WMH had a significant association with incident walking speed limitation occurring over nine years of follow-up (aHR 2.65, 95% CI 1.25-5.61). This was visible in the fully-adjusted model, controlling for age, sex, education, MMSE score, CRFs, *APOE* ε4 status, chronic diseases, and CVDs. The significant association was mainly driven by blood pressure. There was, however, an association between greater SVD burden and limitation in walking speed (aHR 4.20, 95% CI 1.88-9.37). This association demonstrated a dose-response relationship, where with greater burden of SVD there was a higher risk of walking speed limitation, which was mainly driven by WMH. Taking into account death during the follow-up did not affect these associations.

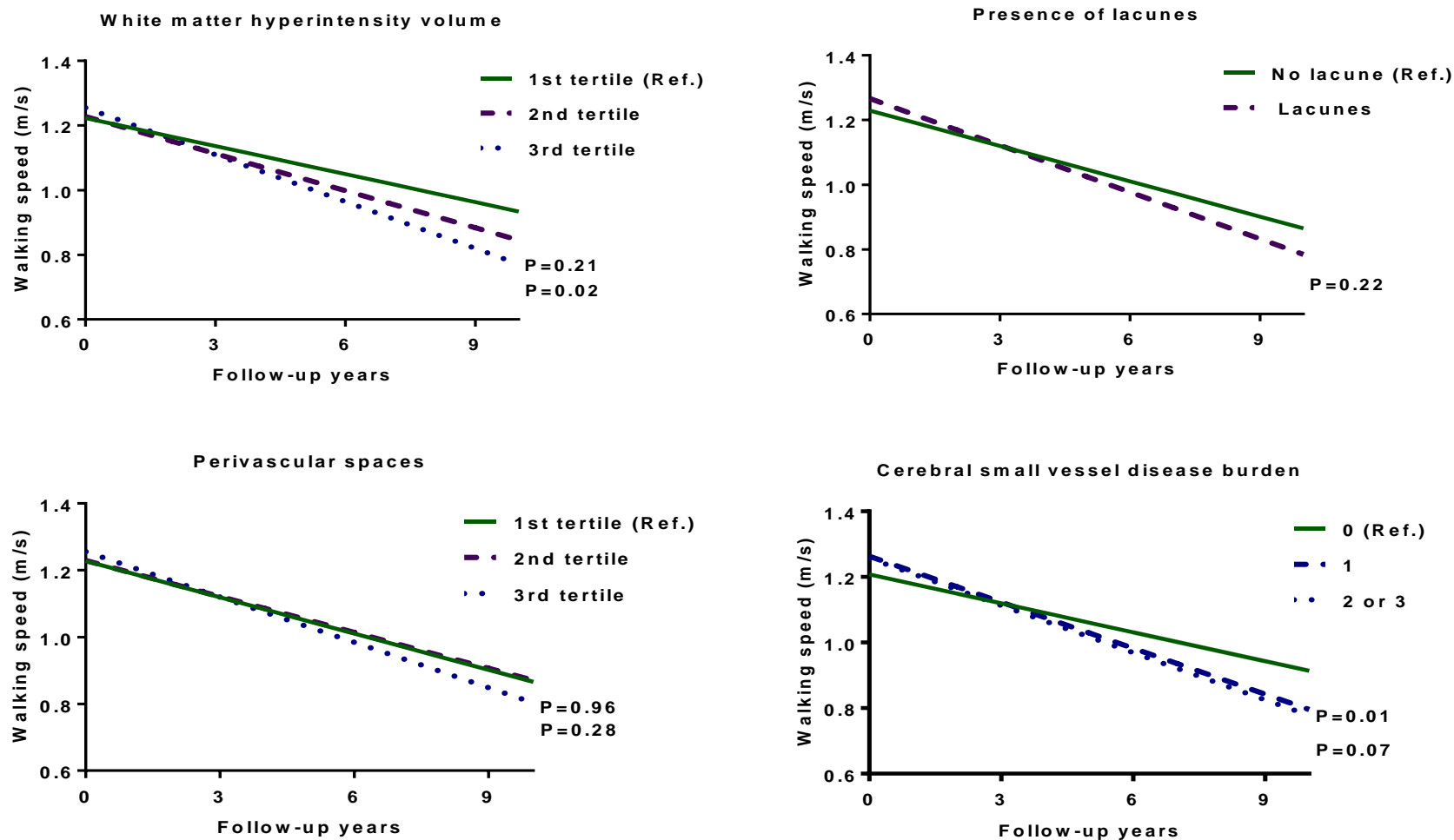


Figure 10. Average annual change in walking speed according to baseline A) tertiles of white matter hyperintensity volume; B) the presence of lacunes; C) tertiles of perivascular spaces; and D) cerebral small vessel disease burden. All models were adjusted for age, sex, education, the Mini-Mental State Examination score, cardiovascular risk factors, *APOE* $\epsilon 4$, chronic diseases, and cardiovascular diseases (n=331).

5 DISCUSSION

5.1 SUMMARY OF MAIN FINDINGS

In this doctoral project, the association between mobility limitation and incident ADL-disability was investigated, as well as the association between CRFs and subsequent physical limitation and disability, in healthy older adults (free of physical limitation, CVD, or both). Furthermore, the possible underlying effect of small vessel vascular pathology, as detected by MRI structural brain abnormalities, was investigated in association with functional limitation. The main findings from this doctoral project are summarized as follows:

- 1) mobility limitation can substantially predict the risk of subsequent ADL-disability, with limitation in walking speed showing a higher predictability than balance;
- 2) CRF burden was associated with a greater risk of walking speed limitation in the younger-old (age ≤ 72 years), but not balance or chair stand limitation, whereas CRF burden was not associated with any physical limitations in the older-old (≥ 78 years);
- 3) multiple CRFs (i.e. physical inactivity, diabetes, and inflammation) seem to play the main role in the increasing risk of ADL-disability among the younger-old, whereas physical functional status (i.e. physical inactivity and walking speed) is more important among the older-old in the development of disability; and
- 4) small vessel brain abnormalities are one of the underlying biological pathways leading to impairment in physical function.

5.2 MOBILITY LIMITATION AND FUTURE DISABILITY

In our population of people aged ≥ 60 years (mean age 73.7 ± 10.8) we found the prevalence of ADL-disability to be 5.0% and the 6-year cumulative incidence to be 6.0%, with an incident rate of 1.5/100 person-years (Study I). In previous cohort studies, prevalence and incidence rates of ADL-disability varied due to heterogeneity in sample characteristics and follow-up lengths. For example, in two rural cohorts of Sweden the prevalence of ADL-disability was 20.5% and 22.8% (190). In the rural Nordanstig cohort of northern Sweden, one of the four centers in the Swedish national SNAC project, the incidence of disability after three years was 10.6%, but after six years was 28.1% in adults 78+, with incidence rates of 5.25 per 100 person-years for disability in at least one ADL (18). This Swedish study also observed a substantial increase in the prevalence of ADL-disability after age 87 years (190), which was similarly observed in our study, where we saw a considerable increase after the age of 84 (Study I). Incidence rates of disability have been reported to range from 5.6-47% in other previous population-based studies (15). For example, in an Italian cohort the estimated incidence was 7.3% over three years for ADL-disability (19). In a Finnish population of adults 60 years and older the incidence rate over five years was 14% (191), whereas in the Health, Aging and Body Composition Study the incidence of disability was 25% over 6 years (139). Similarly, in the Rotterdam study the incidence was 26.7% over six years follow-up (15). Another American community-dwelling cohort, Precipitating Events Project, it was reported that 18% of adults 70+ years developed ADL-disability over three years at an incidence rate of 2.5 per 100 person-year (55).

We demonstrated, in study I, that walking speed was the main predictor of ADL-disability in older adults, which was in accordance with other several studies (11,12,14,51,54,55,57,58,192-194), even among high-functioning older adults (45,46). A pooled analysis of seven studies containing 27 220 adults 65 years and older, showed that walking speed was a significant predictor of incident disability (192). In regards to the relationship between walking speed and balance and future disability, it has been mainly observed that balance is of lower predictive value than walking speed in functional decline. One study of Japanese older adults showed that the balance test had the second highest predictive value after walking speed for functional dependence in adults age 75 years and older (14). Comparably, the tests that reflect balance and control became non-significant predictors of ADL-disability when added in the model with walking speed in a Norwegian study (12). However, conflicting results have also been reported, such as one study in the US showing balance to be a stronger predictor of ADL-disability than walking speed over 18 months in adults with an average age of 80.3 years (16), and another study of Japanese adults 65-74 years old where the one-leg balance stand test was a stronger predictor of ADL-disability than walking speed after six years of follow-up (14). In the American study the reason balance demonstrated a stronger predictability than walking speed was due to the more complex nature of the test administered. However, in the Japanese sample, where the same test was used as in this thesis, this may reflect the early decline in balance prior to walking speed, as balance's stronger predictability was only evident in younger-old adults, but not the older-old.

Few studies have taken into consideration the temporal and predictive hierarchy of physical functioning decline, where balance deteriorates prior to gait or displays a weaker predictive value for disability. Indeed balance is also an important component of completing daily activities, deteriorating also with age (195), with its diminishment further affecting the course of disease to disability (196). Therefore, balance adds worth in identifying the early markers leading to the loss of independence. Furthermore, biomechanically, balance is a chief constituent and prerequisite of human gait. Standing balance involves sensory input and neuromuscular control, so that perturbations on the body, such as in walking, requires greater effort for one to maintain their center of gravity within their base of support (197,198). Thus, impairment in standing balance may indicate changes in the muscular and neurological systems that may occur prior to walking speed impairment (197,199).

Walking speed, one of the most informative measures of health and strongest predictor of future adverse health events. Walking requires a combination of multiple systems to work simultaneously, such as cardiovascular, neurological, and respiratory. Any slight disruption in these biological systems will directly affect gait and manifest in a slowed speed, even without overt diseases. Walking speed has been repeatedly used, displaying independence in predicting disability, even demonstrating superiority to a whole battery of tests, and capability to predict survival (40,43,192,200). Although, walking speed is a great indicator of future health events – as reported in one review of 12 studies, where walking speed was presented as the most powerful indicator of disability (79) – other physical functions can give us even more information for early detection of risk of disability, as we showed in the combined effect of balance and walking speed limitation (Study I). Therefore, this project highlights the usefulness of other tests, such as the simple one-leg balance stand test, in being an early indicator of high-

risk older adults to prevent the risk of disability, and also emphasizes the aptness of the walking speed test in providing even more information.

5.3 CRFS AND PHYSICAL FUNCTION LIMITATION AND DISABILITY

CRFs are important risk factors for an underlying cardiovascular pathology that has not yet manifested overtly as CVD. It has been reported previously that CVD is the most common disorder in the SNAC-K population among those 75 years and older (39.9%) (201) and CRFs are highly prevalent (85). The results from this doctoral project show how these modifiable risk factors can be detrimental to an older adults' physical health and increase their risk of developing disability even among relatively healthy older adults. Earlier studies have also noted the association between individual CRFs and physical function (62) (See Table 2 in the Background). However, most studies did not exclude those with chronic conditions especially with regard to CVD. As well, walking speed has been mainly investigated, showing that high cardiovascular risk can lead to a slower walking speed, while other physical functions have been neglected or chiefly included in physical performance batteries, rather than teased apart.

We showed evidence that CRFs seem to play a more important role in the decline in walking speed than in other physical functions, such as balance and muscle strength (Study II). As well, this was independent of other chronic conditions and cognitive function, and was observed in a healthy older population. A decline in walking speed illustrates deficiencies in several organ systems (i.e. neurological, cardiovascular, respiratory). Thus, walking speed is not only a measure of physical function, but also of subclinical conditions (202). This again reinforces the importance of the walking speed test as a tool to detect older adults at risk of losing their independence and decreasing quality of life. CRF burden did show an association with future poor balance initially (Study II), but this association disappeared after controlling for other lifestyle factors, inflammation, and cognitive function. Plus, when examining the individual vascular factors, most showed no association with balance in our older adult population. Thus, this affirms that disruptions in balance are less affected by changes in the cardiovascular system, as depicted in walking speed, but rather balance is more influenced by weakening in sensory systems. Furthermore, similar CRFs (e.g. physical inactivity and diabetes) found to predict disability in study III, also predicted walking speed limitation in study II, hence suggesting that the underlying pathology leading to walking speed decline is more similar with disability than balance's underlying pathology.

Earlier studies have also reported the association between individual CRFs and the development of disability (See Table 2 in the Background), as we have observed (Study III), although, we observed this in a healthy older population. Additionally, there was a modifying effect of walking speed on the association between some CRFs and disability, such that there was a greater risk in those who also had walking speed limitation (Study III). This has not been previously investigated, but emphasizes the similar pathway in the progression from physical limitation to disability. Thus, it is important to concentrate on both physical and cardiovascular factors in order to help older adults maintain independence longer.

5.4 INDIVIDUAL VS. COMBINED CRFS

We found that a combination of CRFs can give us a good picture of the risk of future poor physical function, but its individual components can elucidate additional information so that effective interventions for the prevention of physical limitation can be developed. Specifically, we found that physical inactivity, diabetes, current smoking, and obesity were associated with increased risk of walking speed limitation over the follow-up (Study II), which is in line with other studies (107,135,149). We only observed this in a sample of 60-72 years old. Other samples of other studies were predominately younger (e.g. middle age) than our sample. The association between physical inactivity and disability has also been repeatedly demonstrated in previous literature, and shown to be one of the fundamental factors in the progression to disability (96).

The concomitant effect of CRFs on physical function in older adults has been little investigated (130,132,134), although older adults are more likely to experience multiple conditions simultaneously (203). One study examined the FRS in relation to physical limitation in a middle-age population (204). This study also found the FRS to be most strongly associated with walking speed limitation, and less with the other physical functions. Another metric, the American Heart Association's Life's Simple 7 (205), which includes seven cardiovascular health factors, also demonstrated that ideal cardiovascular health can decrease the risk of physical limitation (131,132,134). However, this algorithm, includes other factors (e.g. diet) and is not as well-established than the FRS. It also does not assess risk, but rather the protective nature of the cardiovascular factors. Our study adds to the literature, the association between aggregated CRFs and various physical function tests of the lower extremities, to give a more holistic picture, to evaluate where efforts should be directed.

5.5 VARIATIONS BY AGE

Age appears to have an impact on the association between physical limitation and incident disability (Study I), but also on the associations between CRFs and physical limitation and disability (Studies II & III). However, there is a paucity of studies investigating variations by age and the age-effect remains under debate. We found that the association between mobility limitation and ADL-disability was stronger in the younger-old (age <78 years) (Study I), as well as the association between CRFs and walking speed limitation and disability (Studies II & III), whereas in the older-old physical decline might be most crucial than underlying alterations in the vasculature. In study II we utilized the FRS, which was originally developed for adults younger than 75 years, which may account for the age differences, however, we believe there is still an age effect, as observed in the other studies in this thesis and from other literature. In a population of older Japanese adults, they found that over the six year follow-up, one-leg balance stand test was the most sensitive predictor for disability among those 65-74 years old, but walking speed was for those 75+ (14). This supports the idea of physical function being more important in the older ages. As well, age variation was also observed for diabetes and disability in women from the Study of Osteoporotic Fractures, showing a significant association between diabetes and incident disability only in women 65-79 years old and not ≥ 80 years (136). Comparably, another study found an association between subclinical cardiovascular abnormalities and physical limitation over time, but not with ADL-disability among adults 40-80 years old free of CVD (206). They found that the association between

subclinical cardiovascular abnormalities and physical limitation was only present in the younger-old, which is in line with our results.

Potential reasons for these age differences are not only due to variations in the measurement tools, but also partly pertaining to the concept of “adaptation” or the protective nature of CRFs in older age. The idea of “adaptation” is in regards to changes occurring from a restriction in blood supply among the older-old, where a limited blood supply is compensated for by distal autoregulatory dilation (206). The findings of the present study suggest that the younger-old are still undergoing a process of adaptation, whereas the older-old have adapted to a restricted blood supply, thus physical function is not as affected. Moreover, other studies have also exhibited an opposite effect of some risk factors on adverse health outcomes in the older-old, presenting a more protective effect. For example, alcohol consumption, hypertension, and BMI have demonstrated a J or U-shaped association with risk of CVD, cognitive impairment, and physical dysfunction in some studies (175,207-209). Therefore, although these factors might have a risky effect in middle-age or younger-old age, they could become protective factors in old age. This might also explain the lack of associations between some CRFs and functional limitation among the older-old.

It has also been proposed that CRFs may be instead markers of robustness, i.e., not being frail. One study of adults 65 years and older in the US, showed that the association between blood pressure and mortality decreased with age, but the prevalence of frailty increased with age (210). Among the oldest adults it is common that blood pressure decreases and low blood pressure has been shown to be associated with increased risk of mortality (175). Plus, another study showed that blood pressure did not predict mortality among healthy adults 75 years and older (113). This is explained by low blood pressure in frail older adults being an indicator of an imminent critical event (e.g. heart failure and death), however, not among healthy older adults (113). The Study of Osteoporotic Fractures including women 65 years and older also demonstrated that diabetes was not associated with physical dysfunction in healthy women 80 years and older, over 12 years of follow-up (136). Thus, the lack of an association between CRFs and physical limitation and disability in the older-old, observed in this thesis, is more likely a result of them being robust, healthy older adults where CRFs do not increase the risk of negative health events.

5.6 BIOLOGICAL MECHANISMS

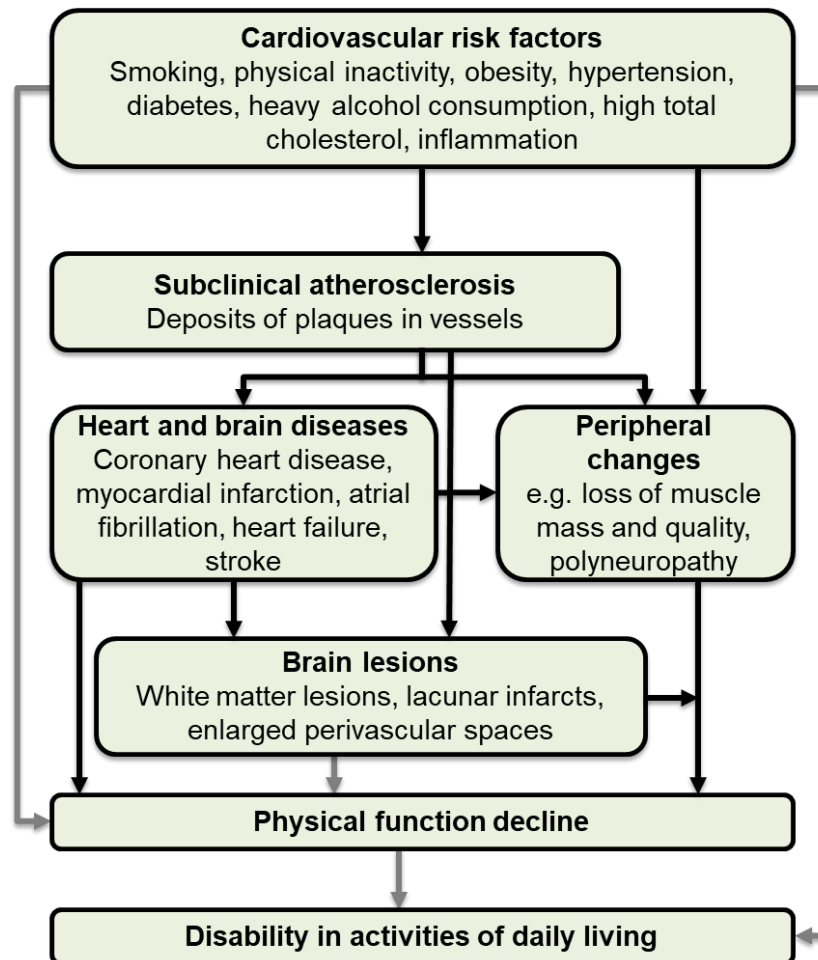


Figure 11. Potential pathways linking cardiovascular risk factors to physical function decline and disability in older adults.

The underlying biological pathways linking CRFs to physical function decline and disability are displayed in **Figure 11**, extending from the WHO's ICF framework, focusing on the medical and biological perspective aging. The changes in physical function that occur with aging can be affected by an underlying cardiovascular pathology instigated by poor lifestyle and cardiometabolic profiles, promoting the atherosclerotic process. In turn, this can damage central and peripheral systems, consequently, either directly causing physical dysfunction and increasing the risk of disability, or going through age-related injury to the brain, subsequently impairing physical functions and accelerating the development of disability. In this thesis we were able to study the associations depicted with the gray arrows.

5.6.1 Atherosclerotic process and peripheral changes

The underlying process by which CRFs increase the risk of CVD is through atherosclerosis, which is also believed to primarily explain the decline in physical function and disability. We found that some specific CRFs were more associated with future functional limitation than others, such as physical inactivity, diabetes, smoking, and obesity. Furthermore, improvements

in these CRFs will also produce favourable effects on each other by enhancing health of the cardiovascular system and also cause peripheral changes. For instance, increasing physical activity will also prove beneficial for blood pressure, cholesterol, insulin sensitivity, and inflammation, among other factors. Also, independently, physical activity, boosts physical function by positively effecting cardiac function by improving myocardial contraction, myocardial oxygen supply, and electric stability, but also promotes increased muscles mass, strength, and quality, and production of pro-inflammatory myokines (83,211). Smoking has substantial negative effects on vessels and also on the musculoskeletal system and it is known that cessation can immensely reduce the risk of CVDs, which in turn can have a positive impact on physical abilities. Diabetes also is known to have significant negative effects on physical capabilities. Diabetes damages muscle tissue and is associated with obesity and increased inflammation (117). Consequences of long-term diabetes are peripheral neuropathy and peripheral arterial disease causing impairment in skeletal muscles and muscle atrophy, but also increased protein degradation and decreased protein synthesis, as well as mitochondrial dysfunction and oxidative stress (147).

5.6.2 Inflammation and cognitive function

Low-grade chronic inflammation is also a common characteristic of the aging process, also termed “inflammaging”, but can have detrimental consequences (137). CRP is one of the most common markers of inflammation and has been shown to lead to vascular damage and insulin resistance (137). Thus, our study adds to the literature showing an association between CRP and disability (Study III), however, not with the physical performance tests (Study II). Yet, inflammation is known to augment the atherosclerotic process (117), and is linked with loss of muscle mass and strength, termed sarcopenia. Also, with age there is fat accrual, in turn increasing the risk of other risk factors, such as diabetes, hypertension, and dyslipidemia. These may act synergistically leading to adverse health events. Fat accumulation can cause dysregulation of adipokines and infiltration of macrophages and other immune cells, producing pro-inflammatory cytokines and chemokines, leading to inflammaging. In turn, sarcopenia and insulin dysfunction can develop. Obesity leads to a heightened production of fatty acids that can accumulate in skeletal muscle as intramyocellular lipids (IMCLs). These IMCLs damage contractility of muscle fibers, reducing strength and power. They also impair fatty acid oxidation and increase reactive oxygen species leading to apoptosis (cell death) of muscle cells, thus a main agent in the pathogenesis from obesity to sarcopenia (212).

Cognitive function has also been suggested to be a possible reason for the association between CRFs and physical function, as CRFs also are associated with worse cognitive performances. Additionally, it is a well-known relationship between cognitive performance and gait, demonstrating a need for higher order cognitive performance (213). Furthermore, there is a suggested similarity in the underlying decline in physical and cognitive function with age (214). However, the associations between FRS/CRFs and physical limitation and disability remained after controlling for cognitive status (Studies II & III). Comparably, in the Whitehall II cohort, their association between the FRS and motor function decline also was not explained by cognitive function (130).

5.6.3 Cerebral small vessel disease

The relationship between CRFs and physical function, may also be partly explained by underlying structural brain abnormalities that occur with aging, such as cerebral small vessel disease (SVD). Although not necessarily pathological, these abnormalities are of vascular origin and potential mediators on the pathway leading to functional decline, hence genuine preclinical conditions. Previous studies have indicated a potential mediating effect of markers of SVD on the association between CRFs and future physical function (115,215,216), suggesting that brain abnormalities are possible mediators on the pathway from subclinical cardiovascular pathology to physical limitation and even disability. A study, however, did find that WMH did not mediate the association between hypertension and walking speed decline (114), but this was explained by the issue of timing, as the exposure and mediator could be measured too closely in time to apprehend a mediating effect. For example, high blood pressure is shown to have an incubation period of five years prior to noticeable changes on organ systems. In our sample we were not able to do a mediation analysis to confirm this hypothesis due to relative small MRI sample and weak associations between CRFs and physical limitation, however, the lack of associations was possibly due to the fact that our sample was quite healthy and that the adverse health impact of certain CRFs (e.g. high blood pressure, high BMI) may decrease or even reverse as people age, as explained earlier (see section “Variation by age”). Nevertheless, the link between long-term exposures and CRFs from middle age onward with cerebrovascular damage (e.g. SVD) has been well established, and we do find an association between different markers of SVD and global SVD burden and a decline in walking speed over time.

The exact mechanisms by which SVD disturbs motor function in the vascular pathway is unclear. It is hypothesized that SVD negatively affects structures of the brain required for motor function. For instance, WMH are presumed to disrupt the sensorimotor tracts in cortical and deep matter regions (159,217). Projection fibers, commissural fibers, and association fibers are believed to be disrupted by WMH leading to physical dysfunction (159). These fibers communicate with sensory processing areas needed for planning and the executing of locomotor functions in the parietal lobe and basal ganglia (159). Specifically, WMH in the periventricular regions are believed to be most damaging (218). Also, recently studies suggest that microstructural integrity of white matter, measured with fractional anisotropy, may be the reason linking white matter changes and mobility decline. One study found an association between more WMH and slow gait in older adults with low integrity of the white matter (219).

5.7 METHODOLOGICAL CONSIDERATIONS

The SNAC-K population study is a large population-based study with a generous sample size, comprehensive data, objective measures of physical function, and assessments carried out by trained health care professionals. However, like every epidemiological study, issues of random and systematic error may arise. Specifically, random error from sampling and measurements, and bias concerning selection, information, and confounding are of most consideration. Our studies were designed and the methods chosen in order to reduce potential bias as much as possible and consequently to increase their internal validity.

Random error

Random error or lack of precision often occurs in epidemiological studies from population sampling and measurements. Sampling variance results from the sample not mirroring the population due to heterogeneity in the population. This error can be reduced by increasing the sample size to improve homogeneity and precision. Measurement error arises from random variation in measurements. For example, the walking speed test was only performed once in our study during each assessment. Repetition of the test may decrease the random error, however, it has been previously reported that even among stroke patients one measure of walking speed is reliable (220), thus we assume minimal error in our studies.

Selection bias

Selection bias can occur from the recruitment of individuals into the study or from the plausibility of retaining them in the study. This bias can usually lead to an underestimation of the examined associations, because the sample selected often does not reflect the population from which it was drawn. In the recruitment an imbalance can manifest in the association between the exposure and outcome due to the procedures of selection and from factors associated with the participants. Also, differences can occur between those who participated in our sample and all those who were eligible, including those who did not participate, leading to bias. However, prospective studies have the advantage of minimizing this bias, because the exposure is measured at baseline, prior to the outcome. As this is a longitudinal study, participants are likely to drop-out for various reasons, such as from moving away or death. In turn, this can impact the results, because characteristics of those who dropped-out during the follow-up and those who remained until the event or the study end may differ. In SNAC-K, the response rate at baseline 73.3%, which is considered high. The drop-out rate at 3-years was 37.3%, and this was mainly in the older age cohorts and due to death (27.6%), while only 9.6% declined to participate or moved. The drop-out rate at 6-years was 25.8%, of which 14.6% died and 11.2% declined or moved. At 9-years the drop-out rate was 30.8% of which 23.5% died and 7.3% were nonparticipants. Therefore, the predominate reason for attrition was death. Drop-outs during the follow-ups in all studies could thus lead to an underestimation of the true strength of the association. Overall and as expected, the characteristics of those who refused to participate and those who moved away or died, compared to those who remained, were more likely to be older, women, and have lower education.

In studies I-IV missing data were taken into consideration either through the dummy variable method or multiple imputation by chained equation (189). This was used to evaluate how

missing data might affect the observed findings. Overall, the results were similar between full case analysis and imputed analyses, suggesting missing data had no significant impact on the results from the analytical sample.

Information bias

Measurement error or inaccurate assessment of exposures, outcomes, or covariates can lead to information bias in epidemiological studies. In turn, misclassification of the main variables utilized in the main analyses can transpire. To avoid or reduce systematic error, study nurses and doctors underwent training prior to data collection to ensure that they followed the same procedures during repeated interviews and assessments. Standardized study protocols, procedures, and diagnostic criteria were used, and the data collection staff turnover was low.

Misclassification of exposures: Information on CRFs were collected through various sources to minimize the information bias. For example, information on behavioural CRFs (physical activity, alcohol, and smoking) were collected by trained nurses through structured interviews. If the participant was unable to respond, such as due to cognitive impairment, next-of-kin was interviewed instead. Although, proxy interviews may relay inaccurate data, the use of multiple sources helped to minimize the bias. Cardiometabolic risk factors, such as hypertension, diabetes, cholesterol, and obesity were gathered from face-to-face interview-based questionnaires, national patient register, drug use, clinical examination, and blood tests. Structured interviews are of higher quality and validity than self-administered questionnaires, but also even with interviews, participants are likely to misreport behaviours. For brain measures, while standard assessment protocols and validated rating scales and approaches have been followed, brain disorders may have influenced the calculations of volumes, therefore we excluded those who had relating brain disorders from Study IV.

Misclassification of outcomes: Physical function and disability were objectively assessed by trained nurses who followed a specific protocol that has been used repeatedly in other studies. These tests were however only performed one time per visit. Random measurement error might have been reduced if the test was repeated several times. Walking speed was measured with standard protocol, therefore systematic error was lessened, however, bias may arise due to the differences in walking distance. Those who reported a usual fast pace were tested over 6 m, while those who reported a slow usual pace were tested over 2.44 m. Notwithstanding, the results of the two tests have been shown to be comparable (221). ADL could have been affected by false recall of participants, however in the interview after the participant reported their ADL status, the nurse also reported whether they agreed/disagreed with the participant's response. If the nurse was unsure about the participant's judgement, they contacted a proxy. This occurred especially in cases where the participant had cognitive impairment.

Confounding

Confounding pertains to the independent association of the exposure and the outcome each with a third variable. The confounding associations are not causal, but if a confounder is not accounted for, it may lead to either an overestimation or underestimation of the observed effect. Although, impossible to control for unmeasured or unknown confounders (residual confounders), because of lack of information or deficient assessment, we carefully chose and

assessed major potential confounders in each of the four individual studies included in the thesis, and proper assessment methods were undertaken.

Generalizability

Generalizability, also termed external validity, pertains to the transferability of the results to other populations in order to make unbiased inferences. The SNAC-K population abides in an urban area on an island in Stockholm. Residents in this area are characterized as having a high level of education and mainly in white collar occupations. Therefore, we can expect this population to have a lower risk of chronic conditions and disability compared to the national average. However, the results do provide us with important information regarding older adults' health in general. Although, greater attentiveness may be necessary when comparing to populations with lower socio-economic status or countries with different healthcare systems. Furthermore, the SNAC-K MRI sample requires also special consideration as this sample's demographics differ slightly. This sample is characterized as being more likely to also have a high education, but more likely to be younger and men. Thus, these characteristics need to be acknowledged when comparing to other study populations.

6 CONCLUSIONS

1. Walking speed is a strong predictor of future disability, however, when combined with balance function, a greater understanding of future functional dependence can be gained.
2. An increasing burden of CRFs is associated with increased risk of limitation in walking speed among older adults free of CVD and physical limitation, suggesting that interventions targeting multiple CRFs simultaneously may potentially decrease the risk of physical limitation and disability among relatively healthy older adults.
3. Modifying cardiovascular health may be most important for the younger-old in decreasing the risk of physical limitation and disability; whereas improving physical function is more important for the older-old, in high-functioning older adults.
4. Vascular brain lesions substantially contribute to an accelerated decline in walking speed as one of the main underlying pathologies.

7 RELEVANCE AND IMPLICATIONS

Remaining functionally independent and having a good quality of life into old age is more fundamental to older adults than longevity. Moreover, with the increasing aging population we not only expect an increasing proportion of older adults, but also a colossal number of those requiring care. The risk of disability increases with age and can be burdensome for the individuals, but coupled with the projected rise in the older population this will also become cumbersome for families, caregivers, and the society. Disability is considered the main reason for increases in healthcare costs. Thus, this project is highly relevant in discovering meaningful points of intervention, in order to implement effective public health strategies. It is paramount to understand functional decline at the early stages and those factors that can accelerate the progression to physical impairment and disability that are in line with the underlying biological pathway. CVDs persist as the leading causes of death globally and even so among older adults and our studies show that CVD-related risk factors are drivers of loss of physical function and independence. Our results show that disability may be more effectively delayed if efforts in developing interventions are made towards reducing cardiovascular risk in the younger-old adults, and towards improving physical functions more in the older-old. Thus, at the public health level and in the development of health policies, means of improving cardiovascular health and physical capabilities to lengthen an older adult's time of independence should be integrated.

Furthermore, in clinical and epidemiological settings, we support the use of easily administrable mobility tests as means of detecting older adults at risk. These tests not only provide information regarding underlying pathology, but can help identify stages in physical decline, as balance, for instance, declines prior to walking speed. Thus, these pragmatic performance tests can provide essential information to the clinician when assessing geriatric patients in order to decide what further assessments are necessary. Furthermore, neuroimaging technology can provide us with deeper information regarding the subclinical changes occurring that could induce the progression further. Thus, clinically, this project highlights the need for use of physical function tests and MRI-imaging to comprehend not only the physical status, but underlying pathologies arresting physical function and accelerating the progression to disability to identify older adults at risk early. Consequently, these studies can provide insight at both the individual and societal level.

8 FUTURE DIRECTIONS

In this doctoral project comprehension was obtained concerning the association between CRFs and future physical limitation and disability, and the association of markers of SVD with walking speed decline. Further studies are required to gain greater insight concerning the involvement of CRFs and biological pathways in the development of physical limitation and its progression to functional dependence in older adults. Specifically, a large-scale population-based study that integrates both epidemiological and clinical data assessed at middle age and later in life with objective measures of physical functioning and imaging markers of brain lesions will help gain a greater understanding of the underlying biological mechanisms and the role of CRFs and SVD on the progression from physical limitation to disability. This would allow for stratification by age cohorts, as well, as investigation into differences by chronic conditions (e.g. exclude /include those with CVD).

Additionally, various physical functions can be studied in the future to establish their link in the vascular pathway and how they interact with each other to further extend knowledge into the ordering of decline in lower extremity function. In turn, this would allow for interventions to be developed more precisely.

Investigation can also be made into CVD-related genes that may predispose older adults to increased risk of not only CVD, but also physical dysfunction. Thus, genetic risk scores can be created to illuminate the joint effect of putative risk genes and identify older adults at greater risk of disability. Consequently, further investigation can be made into whether CRFs may modify one's genetic predisposition in order to mitigate the negative effects of the risk alleles.

Subsequently, a greater understanding of risk factors and heredity may allow for the development of multi-domain interventions. Randomized controlled trials can be performed to test if we can improve older adults' health and reduce the risk or hinder the onset of physical limitation.

Furthermore, future studies can extend the ICF model to incorporate environmental and personal factors that plausibly influence the transitions in physical function over time, allowing older adults to be functional with technological aids and devices. This might further elucidate a potential integration of medical and social factors. Consequently, this transdisciplinary perspective may aid in reaching the needs of older adults from other angles through therapeutic and preventative interventions not only biologically but also contextually.

9 ACKNOWLEDGMENTS

I am grateful to my main supervisor Associate Professor Chengxuan Qiu for his guidance and support during my doctoral studies. Thank you for always being available and providing feedback promptly. Thanks to my co-supervisor Associate Professor Anna-Karin Welmer for the stimulating discussions and assistance for the furtherance of my education. Thanks also to Professor Laura Fratiglioni for your devotion in giving professional feedback and for giving me the opportunity to work at ARC and in doing so, contribute to the group.

I would also like to express my sincere gratitude to those at ARC/KI who I have encountered at various moments throughout my doctoral education: Vanessa Suthat, Maria Yohuang, Maria Wahlberg, Lena Ragert Blomgren, Cecilia Annerholm, Johanna Bylund, Hélène von Strauss, Zoltan Pethö, Christian Lynghaug, Grégoria Kalpouzos (my first roommate who always highlights fascinating features in the brain), Beata Ferencz, George Samrani (for encouraging me to keep looking up and not around), Lieke De Boer, Neda Kaboodvand, Bárbara Avelar Pereira, Xin Li, Nina Becker, Nicola Payton, Rasmus Berggren, Jonas Persson, Yvonne Brehmer, Erika Jonsson Laukka, Goran Papenberg, Alireza Salami, Lars Bäckman, Alexander Darin Mattsson, Johan Rehnberg, Charlotta Nilsen, Harpa Sif Eyjólfsdóttir, Louise Sundberg, Jonas Wastesson Stefan Fors, Neda Agahi, Ingemar “Pingo” Kåreholt, Josephine Heap, Johan Fritzell, Pär Schön, Anna Laveskog (fantastic teacher and showing me around the Neurocenter), Yajun Liang, Malin Ericsson, Davide Liborio Vetrano, Kuan-Yu Pan, Edwin Tan, Miriam Haaksma, Lucas Morin, Giulia Grande, Barbara Caracciolo, Kim Kane, Sara Angleman, Alessandra Macciotta, Catarina Pirali, Camilla Ferrari, Ying Shang, Weili Xu, Federica Prinelli, Caterina Trevisan, Francesca Mangialasche, Lina Keller, Hui-Xin Wang, Krister Håkansson, Amaia Calderon Larrañaga, Shireen Sindi, Serhiy Dekhtyar, Jonas Wastesson, Björn Karlsson, Pär Lundkvist, Kristina Johnell, and Behnaz Shakersain, Almira Osmanovic Thunström and Babak Hooshmand (who helped me out when I began at ARC), and the NVS PhD Student Council.

Special thanks to Anna Marseglia who is not only a brilliant researcher, but a passionate person and warm-hearted friend who has been by my side (or literally back-to-back), throughout the four years. Thanks for the stimulating and fun discussions – there is never a dull moment! I am glad we could go through this journey together! As well, Mozhu Ding, thanks for your support and kindness, and your fresh perspectives. Rui Wang, my big sister at ARC, who not only was my statistical guide, but encouraged me in my development as a researcher and to not lose sight of what is important. Thanks also for introducing me to climbing! Stina Ek, who has such a wealth of information, and has been on this journey with me since our master program (although with a short hiatus). Thanks for your kindness and patience with my Swedish, for being my training partner and inspiring me with your physical strength! My rapping partner Linnea Sjöberg, thanks also for being part of the journey throughout the PhD and also a strong supporter! Thanks to my roomie Cristina Dintica for your patience and enduring with me. Dominika Seblova, thanks for inspiring me to be adventurous not only in leisure activities, but

also in work. Thanks for reminding me to enjoy the beauty around in nature and not taking things for granted. Giola Santoni and Debora Rizzuto, who I had the opportunity to travel with to a conference in the US and leave ARC stranded without a statistician for half a week, thanks for the both fun and serious discussions, and for looking out for me.

My mentor, Professor Doctor Wolfgang Heide, and his family – I am appreciative of not only your input on scientific and career matters, but also for the spiritual guidance before, throughout, and to the end of the doctoral degree.

My brothers and sisters in Christ, thank you for your continuous prayers, which are the only reason that I can complete this education. Thanks specifically to Ruth, Waldemar and family; Tirza, Stephan, Barbro, Bernth, Victoria, Kavitha (Ely & Eli), Jack, Georges, George, Yike, Benedicta, Selma, Hulda, Laila, Harry, Debora, Pieter, Nienke, Natan, Ladan, Philippa, André, Maria, Marcus, Yarett, Ricard, Bwalya, Rodica, Theo, Magdalena, Henri, Jenny and family, Ingmarie, Bella (Lucas), Ian, Daniel, Yossa, Rachel, Germán, Ezra, Evelyn; Lis, Bogi and family; and friends Farzana (Namirah), Tanjil, and Sam.

“Every good gift and every perfect gift is from above, and cometh down from the Father of lights, with whom is no variableness, neither shadow of turning” (James 1:17). I give thanks primarily to my heavenly Father, who has not only given me life and meaning, but blessed me with the opportunity to work at ARC and encounter my fellow-workers. He has also blessed me with an extremely supportive and understanding family who have given me more love and care than I deserve. Thanks to my parents Hans-Jörg and Hesed, and my siblings, Myles, Vincent, and Carmel. The Lord worked all things together for a harmonious outcome.

I also thank other members of my family who have encouraged me throughout and shown interest in my work. Grandparents: Heinrich and Erika; Darlington and Georgiana; with Abigail, Juliet, Dale, Jemima, Anna, Samuel Sr., Sammy, Simon, Henry, Margit, Hester, Justus, Eberhard, Ulrike, Jörg-Philip, Madeleine, Hanna Lisa, Anne Christin, and Francis.

The PhD student’s learning process was supported by the Swedish National Graduate School for Competitive Science on Ageing and Health (SWEAH) funded by the Swedish Research Council.

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11 APPENDIX

Appendix Table 1. Population-based cross-sectional studies on the association between cerebral small vessel disease and walking speed limitation.

Author, year	Study population	Age	SVD	Outcome measures	Main results
SVD burden					
Su 2017 China (169)	Shunyi study, N=770	35+	WMH, lacunes, CMBs, PVS, and brain atrophy	Walking speed	WMH were negatively associated with walking speed, and positively associated with chair-stand time. Lacunes, CMBs, or PVS were not associated with motor performance.
Pinter 2017 Scotland (168)	Lothian Birth Cohort 1936, N=678	71–74	SVD markers (WMH, microbleeds, lacunes, perivascular spaces, brain atrophy)	Walking speed	WMH and global SVD score were predictors of walking speed.
Individual CRFs					
Baezner 2008 11 European countries (222)	LADIS, N=639	65-84	Age-related white matter changes	Walking speed and balance	Limitation in walking speed and balance performance were associated with the severity of age-related white matter changes.
Rosano 2010 Iceland (223)	AGES-Reykjavik Study cohort, N=795	Mean 75.6	WMH, brain atrophy, brain infarcts	Walking speed	Higher WMH were associated with slower walking speed.
Smith 2015 Canada (224)	Prospective Urban Rural Epidemiological substudy (PURE-MIND), N=803	40-75	Silent brain infarcts-Lacune, CMBs, and WMH	Timed Up and Go test of gait	Silent brain infarcts were associated with slower gait. Higher volume of WMH was associated with slower gait.
Kim 2016 USA (225)	Cardiovascular Health Study, N=2452	65+	Microvascular abnormalities (brain, retina, kidney) and macrovascular abnormalities (brain, carotid artery, heart, peripheral artery).	Walking speed, grip strength, chair stand	Participants with high microvascular and macrovascular burden had worse physical function, then those with low. WMH were independently associated with physical function.
Rosario 2016 USA (219)	Health, Aging and Body Composition (Health ABC) study, N=265	Mean 82.9	WMH	Walking speed on the GaitMat II, an instrumented, computerized 8-m walkway	WMH were more strongly associated with walking speed in those with low fractional anisotropy than those with high fractional anisotropy.
De Laat 2010 The Netherlands (226)	The Radboud University Nijmegen Diffusion tensor and MRI Cohort (RUN DMC) study, N=431	50-85	WMHs and lacunar infarcts	GAITrite, Tinetti and Timed-Up-and-Go test	WMH and lacunar infarcts were associated with most gait parameters, with stride length as the most sensitive parameter related to WMH.
Reviews: Zheng 2011 (153); Kilgour 2014 (157). WMH: white matter hyperintensities; PVS: perivascular spaces; CRF: cardiovascular risk factors; ARWMC: age-related white matter changes; SPPB: Short Physical Performance Battery; OLBS: one-leg balance stand; Cerebral microbleeds (CMBs).					

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Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

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